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Supreme Court of the United States

OCTOBER TERM, 1969

No. 1436

CARTER-WALLACE, INC.,

Petitioner,

v.

ROBERT H. FINCH, SECRETARY OF HEALTH, EDUCATION AND WELFARE, and CHARLES EDWARDS, COMMISSIONER OF FOOD AND DRUGS,

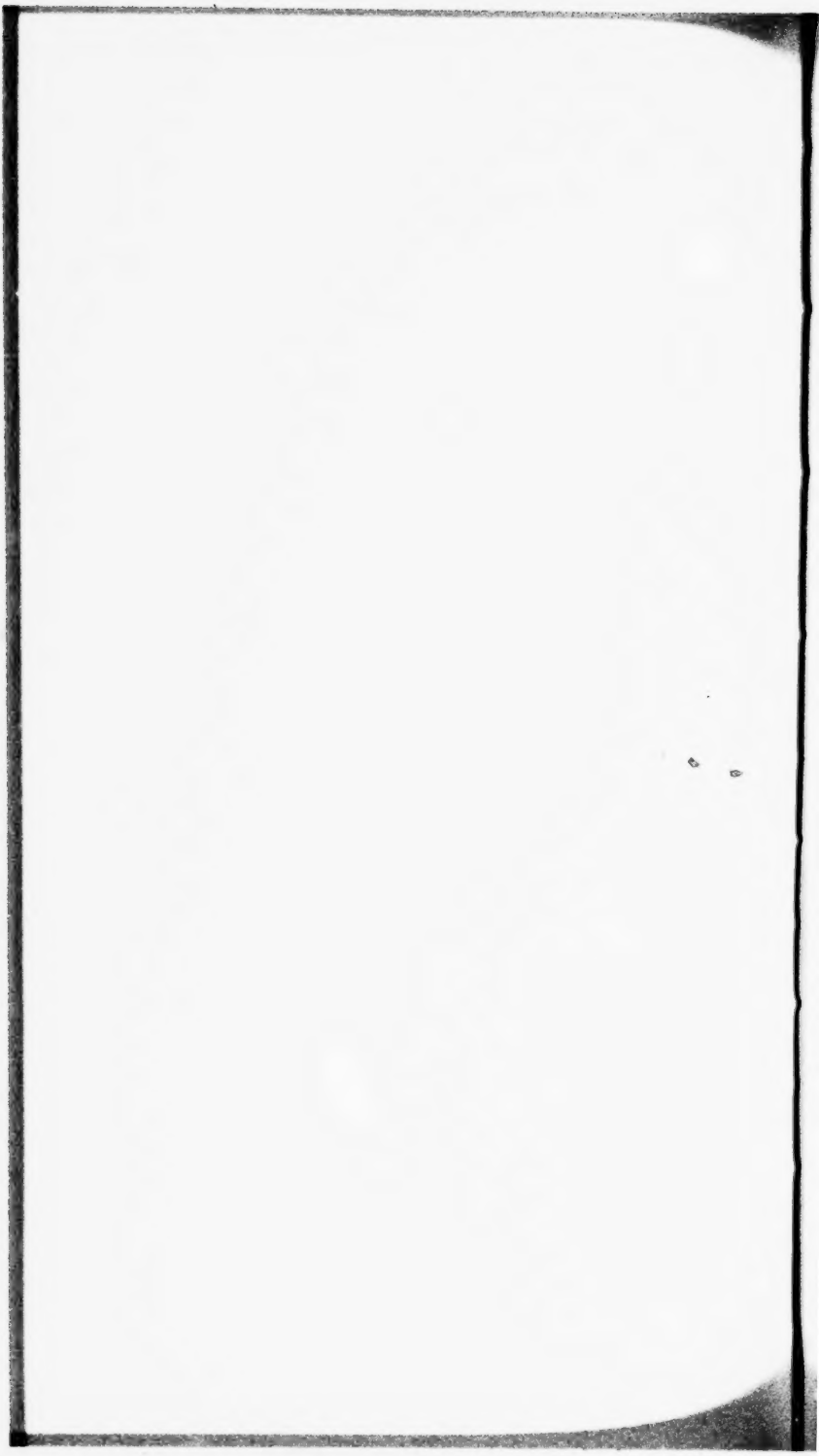
Respondents.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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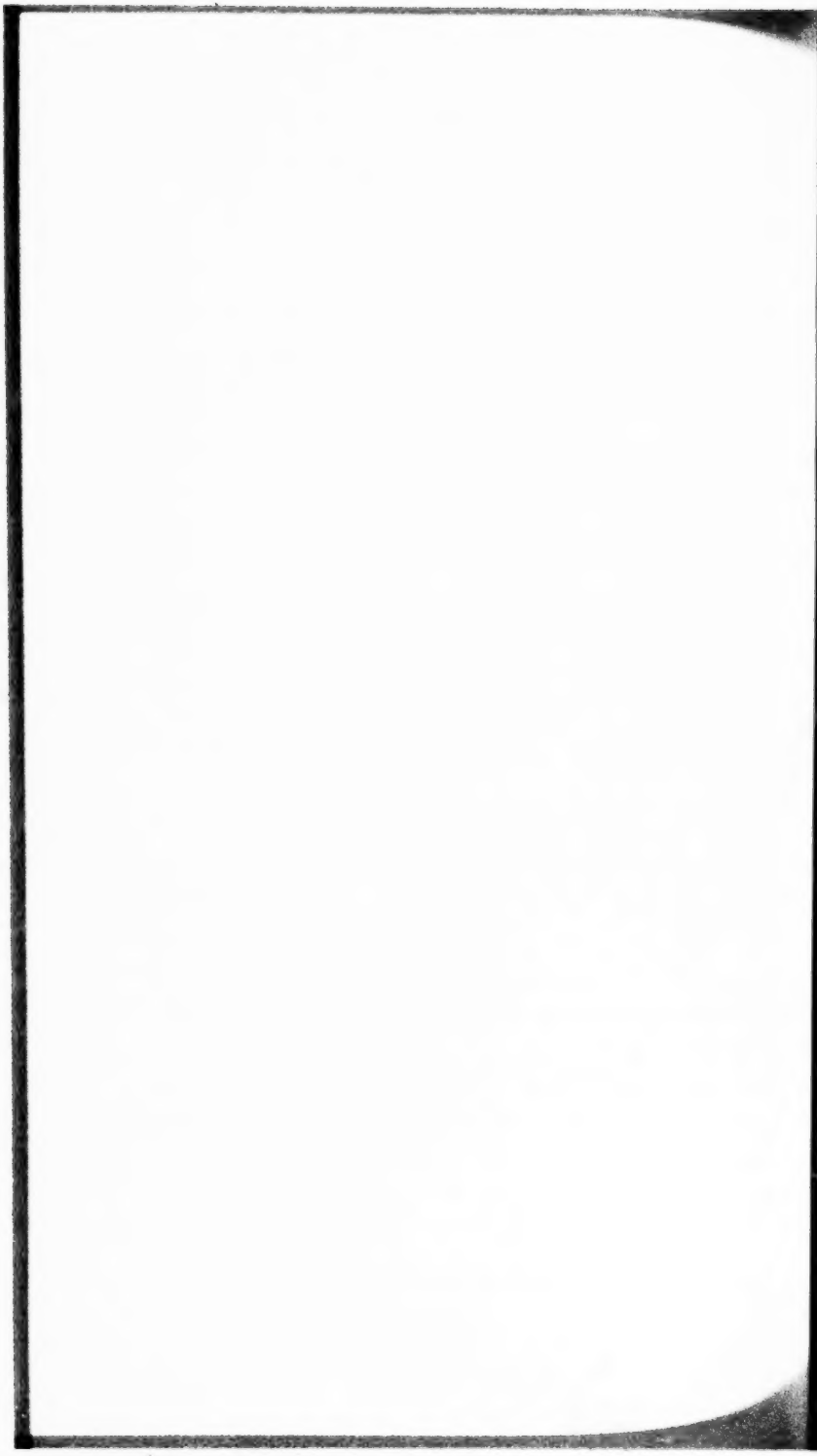
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CARTER-WALLACE, INC.,

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ROBERT H. FINCH, SECRETARY OF HEALTH, EDUCATION AND WELFARE, and CHARLES EDWARDS, COMMISSIONER OF FOOD AND DRUGS,

Respondents.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

Petitioner, Carter-Wallace, Inc., prays that a writ of certiorari issue to review the decree and opinion of the United States Court of Appeals for the Fourth Circuit.

Opinions Below

The opinion of the Court of Appeals, reported at 417 F.2d 1086, is in Appendix A (p. 1a, *infra*). The opinion of the Hearing Examiner is in Appendix B (p. 20a). The Findings of Fact and Conclusions of Law of the Commissioner of Food and Drugs is in Appendix C (p. 35a).

Jurisdiction

The decree of the Court of Appeals for the Fourth Circuit was entered on November 25, 1969. On February 10, 1970, Mr. Chief Justice Burger extended the time for filing a petition for a writ of certiorari to and including April 21, 1970. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

Questions Presented

1) Whether an order of the Commissioner of Food and Drugs, which by statute "shall be based only on substantial evidence of record", can be sustained when the only support for such order is an unverified theory suggested by a single witness, which is in direct conflict with all the evidence in the record.

2) Whether there was proper adherence to "the whole record" requirement for judicial review of agency action.

3) Whether the statute compels the Commissioner to exempt the meprobamate combination products because the Examiner found that such products do not have a potential for abuse.

4) Whether the order as to the meprobamate combination products should be set aside on the ground that the Commissioner failed to make essential findings of fact as to such products.

Statutes and Regulations Involved

The relevant statutes and regulations are set forth in Appendix E (p. 68a).

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Statement

The basis for federal jurisdiction in the Court of Appeals is Sections 201(v) and 701(f) of the Federal Food, Drug, and Cosmetic Act, as amended (the "Act") (21 U.S.C. 321(v), 371(f)), and Section 10 of the Administrative Procedure Act (5 U.S.C. 702, 704, 706).

This is a proceeding to review an order of the Commissioner of Food and Drugs ("FDA"). The order would impose on the drug meprobamate the identical special controls and restrictions as are imposed on barbiturates ("goof balls"), amphetamines ("pep pills"), LSD and other known dangerous drugs. The order, promulgated after an evidentiary hearing, is under the amendments to the Act known as the "Drug Abuse Control Amendments of 1965" (the "Amendments") (79 Stat. 226, July 15, 1965).* The administrative hearing as to meprobamate was the first under the Amendments. This is the first case to review the scope and intended coverage of the Amendments and the validity of an FDA order thereunder. Because of the nature of the FDA findings at issue here, this case involves questions which are of utmost interest and importance to the scientific world.

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* FDA has stayed the order pending "a final judgment in the proceedings for judicial review" (33 F.R. 3635, 3/1/68). The controls imposed by the Amendments are accomplished by limiting the number and time in which prescriptions may be refilled, by requiring a drug abuse symbol on labels and other packaging to advise of the drug's abuse potential, by increased recordkeeping and inspection requirements, by regulation of intrastate traffic, and by making possession of the drug, other than by the user, illegal outside of legitimate channels of commerce (21 U.S.C. 360(a), 21 C.F.R. 166.18, H.R.Rep. No. 130, 89th Cong., 1st Sess., pp. 1, 3 (1965)).

A.

Meprobamate, a prescription drug, is classified as a "minor tranquilizer". It was developed by petitioner in 1952 and approved for sale by FDA in 1955. It rapidly became the most widely prescribed drug for the symptomatic relief of anxiety and tension. Petitioner markets meprobamate under the name "Miltown", and sells meprobamate to other pharmaceutical companies for resale under their own brand names.

The principal target of the Amendments was the amphetamines and barbiturates, which had demonstrated a substantial abuse potential because of their effects on the central nervous system. Not all drugs and not all drug abuse are covered or intended to be covered by the Amendments. Nor does it suffice merely to show a drug has a depressent, stimulant or hallucinogenic effect on the central nervous system. A drug can be listed only if it is found to have, in the words of Section 201(v)(3) of the Amendments, "a potential for abuse *because* of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect" (21 U.S.C. 321(v)(3)).* The need to prove a causal relationship between a drug's abuse potential and its effect on the central nervous system was stressed throughout the legislative history of the Amendments. The House Report** stated that "a drug's 'potential for abuse' should be determined on the basis of its having been demonstrated to have such depressant or stimulant effect on the central nervous system as to make it reasonable to assume there is a substantial potential" for abuse. The Senate Report*** also

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* Unless otherwise noted, italics have been supplied.

** Report of the Committee on Interstate and Foreign Commerce on H.R. 2 (H.Rept. No. 130, 89th Cong., 1st Sess., p. 7).

*** Report of the Committee on Labor and Public Welfare To Accompany H.R. 2 (S.Rept. No. 337, 89th Cong., 1st Sess., p. 5).

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emphasized that the Amendments apply only to drugs which have a substantial abuse potential "because of their depressant or stimulant effect on the central nervous system".

Congress considered the causal relation question of such importance, that it authorized FDA to appoint an independent "committee of experts to advise" on two matters, namely, "(A) whether or not the substance involved has a depressant or stimulant effect on the central nervous system or a hallucinogenic effect", and "(B) *whether the substance involved has a potential for abuse because of its depressant or stimulant effect on the central nervous system*" (21 U.S.C. 360(a)(g)(1)).*

Petitioner and FDA approached the case very differently. Petitioner acknowledged that meprobamate has a selective central nervous system depressant effect, and, like all ingestible substances, has some potential for abuse. The thrust of its case was that meprobamate's central nervous system depressant effect is in no way responsible for or related to its abuse or potential for abuse. Petitioner's medical witnesses, including top-level Government physicians and public health service officials, testified from carefully controlled animal experiments and clinical studies that meprobamate's selective depressant action on the central nervous system cannot possibly contribute to, much less be the cause of, its potential for abuse.

The evidence overwhelmingly demonstrated that the rare incidents of excessive use or other abuse of meprobamate

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* Though FDA appointed an independent committee of experts to consider meprobamate, neither the report of that committee nor its deliberations were introduced at the hearing. After objection to the introduction of a bare summary of the report was sustained, FDA withdrew the summary and moved "that the questions and answers relating to the advisory committee be stricken from the record" (TR. 343).

are not a result of the drug's pharmacological action on the central nervous system. When meprobamate is abused it is for the same reason and by the same type individual who would abuse any number of other ingestible substances which have absolutely no effect on the central nervous system. Quite apart and distinct from the drug addict, who abuses a drug to achieve certain definite non-therapeutic effects, there is another though far smaller group who abuse vitamins, aspirin, candy and virtually any other substance, though there may be no effect, or even a wholly unpleasurable one (TR. 3434-35, App. 514).* In the House hearings on the Amendments, it was pointed out that every drug, and indeed, "Anything that the human body consumes", has some abuse potential.** But Congress emphasized that this was not the type of abuse at which the Amendments were directed. The Amendments were aimed at the drugs which, because of their action on the central nervous system, furnish "kicks", "thrills" or other non-therapeutic effects sought by drug abusers.

FDA did not even attempt to establish a connection between meprobamate abuse and its central nervous system depressant effect. Instead, FDA promulgated a regulation which conclusively presumed that if meprobamate had a potential for abuse, such potential results from its central nervous system depressant effect (p. 77a). Accordingly, FDA concentrated on proving that meprobamate has an abuse potential, ignoring the cause and effect test of the Amendments. FDA called more than 20 physician witnesses on its direct case, but failed to elicit a single

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* References to "TR." are to the original Transcript of the hearing. References to "App." are to the Appendix to Petitioner's Brief printed for use in the Court of Appeals.

** Hearings Before Committee on Interstate and Foreign Commerce of the House of Representatives, 89th Cong., 1st Sess., on H.R. 2, p. 151.

opinion as to whether meprobamate's abuse potential was because of its central nervous system depressant effect. More than 100 medical articles were evidenced by FDA, but none were related to the cause and effect question.

Armed with the regulatory presumption, FDA counsel said "the regulations * * * would apply in this hearing, * * * and FDA would introduce at this hearing evidence under" the regulations (App. 137). FDA reiterated that the "sole issue * * * [is] whether meprobamate is a drug with a potential for abuse" (TR. 1684-85); and that "it is the Government's position that the issue at this trial and this hearing is, does meprobamate have a potential for abuse" (TR. 2495), totally disregarding the need to prove that such potential for abuse is "because of its depressant * * * effect on the central nervous system" (21 U.S.C. 321(v)(3)).

The FDA Examiner also deemed the regulatory presumption to control. He admitted petitioner's evidence that there was no causal relationship between meprobamate abuse and its depressant effect on the central nervous system only to provide "the necessary record to advance this argument" to "a reviewing court", and "to avoid a remand * * * to take evidence on this point" (App. 357, TR. 1974).

Accordingly, it could not be clearer that throughout the hearing, both FDA counsel and the FDA Examiner firmly believed and proceeded on the basis that FDA need prove only that meprobamate had a potential for abuse, without even attempting to satisfy the cause and effect test of the Amendments. In fact, neither the Examiner's proposed findings of fact, dated 4 months after the close of the hearing (App. 49), nor the Commissioner's initial findings of fact, dated 7 months after the hearing (App. 79), contained a finding on the causal-relationship question. It was not until well over a year after the hearing

had concluded, and only after receipt of petitioner's objections to the proposed findings of fact, did FDA expressly find that meprobamate had a potential for abuse because of its depressant effect on the central nervous system (p. 61a).

The cause and effect question was one of the key issues on appeal. The Court rejected FDA's position that meprobamate could be controlled under the Amendments on the mere showing that the drug had an abuse potential. The Court recognized that "to subject meprobamate to the Act's special controls the Commissioner must find" that it has a substantial potential for significant abuse, and "that this potential results from its depressant effect on the central nervous system" (pp. 4a, 8a). The Court further agreed that FDA's regulation and its conclusive presumption "cannot be used to dispense with proof of the causal relationship required by the statute. *Miller* v. *United States*, 294 U.S. 435, 440 (1935)" (p. 9a).

Though FDA had called over 30 witnesses and had evidenced thousands of pages of scientific exhibits in the course of a three-month hearing, the Court could find neither "direct evidence" nor even any "verified theories" (p. 12a) to support the alleged causal relationship. On the other hand, as the Court noted, a "number of well-qualified medical witnesses" testified that there was "no relation between meprobamate's potential for abuse and its depressant effect on the central nervous system" (pp. 6a, 11a).

Nevertheless, the Court held the causal relationship finding was supported by substantial evidence. The "evidence" on which the Court relied consisted of a "theory", which "had not yet been verified", which if ever verified, would relate to the barbiturates and not to meprobamate, which was suggested as a possibility by but one of a total of 50 physician witnesses heard at the hearing, and which was

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in direct conflict with the results of controlled studies and clinical observation by a number of eminent physicians.

The theory was suggested by Dr. Jerome Jaffe, a psychiatrist with extensive experience with the use and effects of barbiturates, but without any comparable expertise as to meprobamate.* He testified that physical dependence on barbiturates may result from changes in the subcortical region of the brain caused by the central nervous system depressant effect of barbiturates. Dr. Jaffe stressed that this was only a theory, and, as the opinion below states, "Emphasizing that his theory of barbiturate dependence had not yet been verified, he suggested that if it is valid for barbiturates, it may be equally valid for meprobamate" (p. 13a).**

The Court of Appeals seemed more impressed with FDA's contention as to the difficulties in establishing the required causal relationship than it was with the alleged evidence of such relationship. For the Court concluded (p. 14a):

> "[*T*]*aking into account our imperfect knowledge of how drugs injure people,* we hold that substantial evi-

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*Dr. Jaffe had not conducted any studies or experiments with meprobamate, controlled or otherwise. On the clinical level, he did not have "the faintest idea" as to the extent of meprobamate abuse (TR. 476). Actually, he knew of only "one case of a patient starting on meprobamate, and then going on to abuse that drug" (TR. 467).

**The Court's only other reference to the alleged causal relationship was with respect to "euphoria", stating that "no evidence was introduced that euphoria results from any effect other than the action of depressant or stimulant drugs on the central nervous system" (pp. 13a-14a). Since there was absolutely no evidence that meprobamate's central nervous system depressant effect caused euphoria, there was no purpose in disproving a contention which FDA was not even making. On the contrary, Dr. Jaffe, FDA's key witness, testified "that nobody knows the mechanism of action of euphoria" (App. 243). FDA's post-hearing memorandum conceded that "euphoria induced by * * * opiates or cocaine [both central nervous system depressants] does not involve depression of the neocortex."

dence supports the Commissioner's finding of a causal relation between meprobamate's depressant effect upon the central nervous system and its potential for abuse."

B.

Petitioner manufactures five meprobamate combination products, "which consist of meprobamate combined with other drugs" (p. 39a). FDA framed the issues so the hearing would cover both meprobamate and the combination products. Petitioner established and the Examiner found (p. 33a):

> "There is a lack of substantial evidence in this record that meprobamate combined with other drugs, manufactured by either respondent or others, have a substantial potential for significant abuse."

The Commissioner made no findings on the combination products. He concluded that combination products are governed by Section 201(v)(3) of the Amendments (21 U.S.C. 321(v)(3)), and all drugs containing any quantity of meprobamate are "depressant or stimulant drugs" by operation of law, and, as such, are subject to the controls of the Amendments. The Court of Appeals agreed (p. 16a).

It is petitioner's position that combination products are governed by Section 511 (f)(2)(B), which provides that FDA *"shall"* exempt any combination product which contains another substance "not having a depressant or stimulant effect on the central nervous system", and which is present in sufficient concentration to prevent the finished drug from having "a potential for abuse" (21 U.S.C. 360(a)(f)(2)(B)). By using "shall" instead of "may", Congress made plain that the exemption is mandatory, and FDA has no discretion once it is found that the finished product does not have an abuse potential. In short, a combination prod-

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uct must be judged by the abuse potential of the finished product, not by a single one of its ingredients.*

Despite the fact the meprobamate combination products were a separate issue at the hearing, and the Examiner affirmatively found such products do not have a potential for abuse, the Court held that the Commissioner's failure to make an affirmative finding of fact as to such products meant that petitioner must initiate an entirely new proceeding for their exemption from the Amendments.

Reasons for Granting the Writ

I.

The opinion below will have important and far-reaching effects on virtually every case involving review of agency action under the "substantial evidence" rule. If, as the Court of Appeals in effect held, the substantial evidence requirement is satisfied by a suggested theory which "had not yet been verified", and which was in direct conflict with the unequivocal and unimpeached testimony of recognized experts, then the substantial evidence rule would become a nullity. It is difficult to conceive of any case in which an agency could not point at least to an unverified theory to support its findings.

It is anomalous and unfortunate that the substantial evidence rule was misapplied in this particular case. Since this was the first occasion in which any governmental body had attempted to determine a drug's potential for abuse, and more important, the pharmacological cause if any for such abuse potential, this case has been and is of vital

* It was established that each of the meprobamate combination products contains another substance which does not have a depressant or stimulant effect on the central nervous system and which is present in sufficient concentration to prevent the finished product from having a potential for abuse (App. 362-63).

concern to a large segment of the medical and scientific community. As one physician at the hearing put it, the mere listing of meprobamate under the same law and bearing the same drug abuse symbol as LSD, goof balls and pep pills, would "produce a catastrophe in American medicine." (TR. 3167). Because of the importance of the scientific questions involved, and because FDA has no expertise of its own in this new area of pharmacology, strict adherence to the substantial evidence rule is especially warranted. This is not a case which should or need be decided by speculation or theory, though the Court below seemed to believe an unverified theory should suffice here "because present medical knowledge has no definitive explanation" for the cause of drug abuse (p. 12a). Such statement disregards the competent and uncontradicted evidence that drug abuse, as that term is used in the Amendments, is caused by drugs which generate certain non-therapeutic effects because of their action on the central nervous system. Meprobamate is not one of those drugs, and there is not a scrap of evidence in the record to the contrary.

Significantly, Dr. Jaffe, the FDA witness on whom the Court relied, demonstrated his concern that his testimony not be misinterpreted. He repeatedly emphasized that his testimony was only a "theory"; "There are a number of theories" on this point (App. 232); "There are a number of studies now under way attempting to verify or refute the theory" (App. 236); and that his "theory tends to encompass [another] theory" (App. 240).*

* After receipt of FDA's proposed findings, which were printed in the Federal Register and circulated by FDA to physicians across the country, Dr. Jaffe wrote the Commissioner to express his concern that his "testimony is being used by FDA—not for the purpose of stating a theory, which was all that was ever intended—but as support for a so-called finding of fact that withdrawal reactions after cessation of meprobamate and tolerance to that drug are definitely due to its central nervous system depressant effect."

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By accepting such wholly theoretical testimony as "substantial evidence", the Court deviated significantly from "the usual rule that evidence * * * by a medical man that a necessary fact is 'possible' or 'conceivable' or 'may be' is not sufficient" (Jaffe, Judicial Control of Administrative Action, p. 598, fn. 6); "Where the opinion of the expert rests upon theories as to which there is no substantial agreement, and is in fact a mere sequence of conjectures, it is of no probative value" (Rogers, Expert Testimony, §135, p. 314 (3rd ed., 1941)); testimony of "a speculative and uncertain nature can afford little, if any, support to findings based thereon" (*Kidder Oil Co.* v. *F.T.C.*, 117 F.2d 892, 899 (7th Cir., 1941)).

The opinion of the Court of Appeals is also in conflict with applicable decisions of this Court, that "Substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Edison Co.* v. *Labor Board*, 305 U.S. 197, 229 (1938). And, as held in *Labor Board* v. *Columbian Co.*, 306 U.S. 292, 300 (1939), substantial evidence "must do more than [merely] create a suspicion of the existence of the fact to be established".

Nor did the Court of Appeals follow "the whole record" requirement for judicial review of agency action (5 U.S.C. 556(d)). Though the Court's opinion notes that a number of well-qualified medical witnesses testified, without challenge or contradiction, that meprobamate's central nervous system depressant effect had no relation to its abuse potential, such testimony was disregarded in favor of a theory

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Dr. Jaffe reiterated that he did "not believe there is medical evidence which 'establishes' that 'meprobamate's potential for abuse results from its effect of depression on the central nervous system' ". Dr. Jaffe's letter is reprinted in the Annex to petitioner's Reply Brief below.

suggested by a single witness. Pertinent is *Universal Camera Corp.* v. *N.L.R.B.*, 340 U.S. 474, 487-88 (1951):

> "Whether or not it was ever permissible * * * to determine the substantiality of evidence supporting a * * * decision merely on the basis of evidence which in and of itself justified it, without taking into account contradictory evidence or evidence from which conflicting inferences could be drawn, the new legislation definitively precludes such a theory of review and bars its practice. The substantiality of evidence must take into account whatever in the record fairly detracts from its weight. This is clearly the significance of the requirement * * * that courts consider the whole record."

The foregoing applies *a fortiori*, since not only did the Court fail to take into account petitioner's evidence, but there was no evidence on the other side "which in and of itself justified" the causal relationship finding. The "assurance of a desirable flexibility in administrative procedure does not go so far as to justify orders without a basis in evidence having rational probative force." (*Edison Co.* v. *Labor Board, supra*, p. 230). That principle should be particularly unyielding where, as here, the administrative determination would have significance far beyond the confines of this one case.

II.

As to the meprobamate combination products, the Court of Appeals held (p. 16a):

> "In this hearing the government was required to show only that meprobamate satisfied the Act's definition of a depressant drug and that the combination drugs contained meprobamate. *Lack of evidence con-*

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cerning the effect of the combination drugs cannot be substituted for the affirmative findings required for exemption."

This misses the mark, for the Examiner did affirmatively find that the meprobamate combination products do not have a potential for abuse (p. 33a).

It is true the Commissioner did not adopt that finding, but neither did he reject it. He made no finding of fact as to the meprobamate combination products—an omission which, instead of prejudicing petitioner and requiring an entirely new hearing as to such products, is itself ground for reversal.

FDA framed the issues for the hearing so as to plainly include not only meprobamate, but the combination "drugs containing meprobamate" (App. 113). The Examiner ruled that petitioner's separate evidence as to the combination products "is within our case" (App. 359). Once the Examiner found from the evidence that the meprobamate combination products do not have an abuse potential within the meaning of the Amendments, the Commissioner had to do one of two things. If he agreed with that finding, the combination products had to be exempted from the Amendments as a matter of law (21 U.S.C. 360 (a)(f)(2)(B)). If he disagreed, then he had to promulgate a new finding of fact which petitioner could challenge for lack of substantial evidence.

In no event can the Comissioner's failure to make a finding of fact serve as basis for controlling the combination products. On the contrary, "In the absence of a finding of essential basic facts, the order cannot be sustained" *Atchison Ry. Co.* v. *United States,* 295 U.S. 193, 202 (1935).

This Court has "repeatedly emphasized the need for • • • basic or essential findings on which administrative

orders rest." *Colorado-Wyoming Gas Co.* v. *F.P.C.*, 324 U.S. 626, 634 (1945); *Securities and Exchange Commission* v. *Chenery Corp.*, 318 U.S. 80, 96 (1943); *United States* v. *Carolina Carriers Corp.*, 315 U.S. 475, 489 (1942); *Florida* v. *United States*, 282 U.S. 194, 212, 215 (1931).

It is now fundamental that where basic findings are lacking, the reviewing court will not search the record for evidence to support the agency's decision:

> "In the absence of such findings, we are not called upon to examine the evidence in order to resolve opposing contentions as to what it shows or to spell out and state such conclusions of fact as it may permit. The Commission is the fact-finding body and the Court examines the evidence not to make findings for the Commission but to ascertain whether its findings are properly supported" (*Florida* v. *United States, supra*, p. 215).

The meprobamate combination products were the subject of an exhaustive administrative hearing. If such products can be controlled under the Amendments merely by reason of the control of the meprobamate ingredient, then Section 360 (a)(f)(2)(B), which is specifically directed at the combination products, is rendered totally meaningless.

It bears reiteration that this is the first case to involve an interpretation of the Drug Abuse Control Amendments. The application of the Amendments to combination products is particularly important, since more and more pharmaceutical companies are developing combination products which contain ingredients in such quantity or proportion as to effectively preclude the possibility of abusing the finished product. Future administration of the Amendments will be greatly facilitated by a definitive interpretation of their scope and coverage by this Court.

CONCLUSION

The petition for a writ of certiorari should be granted.

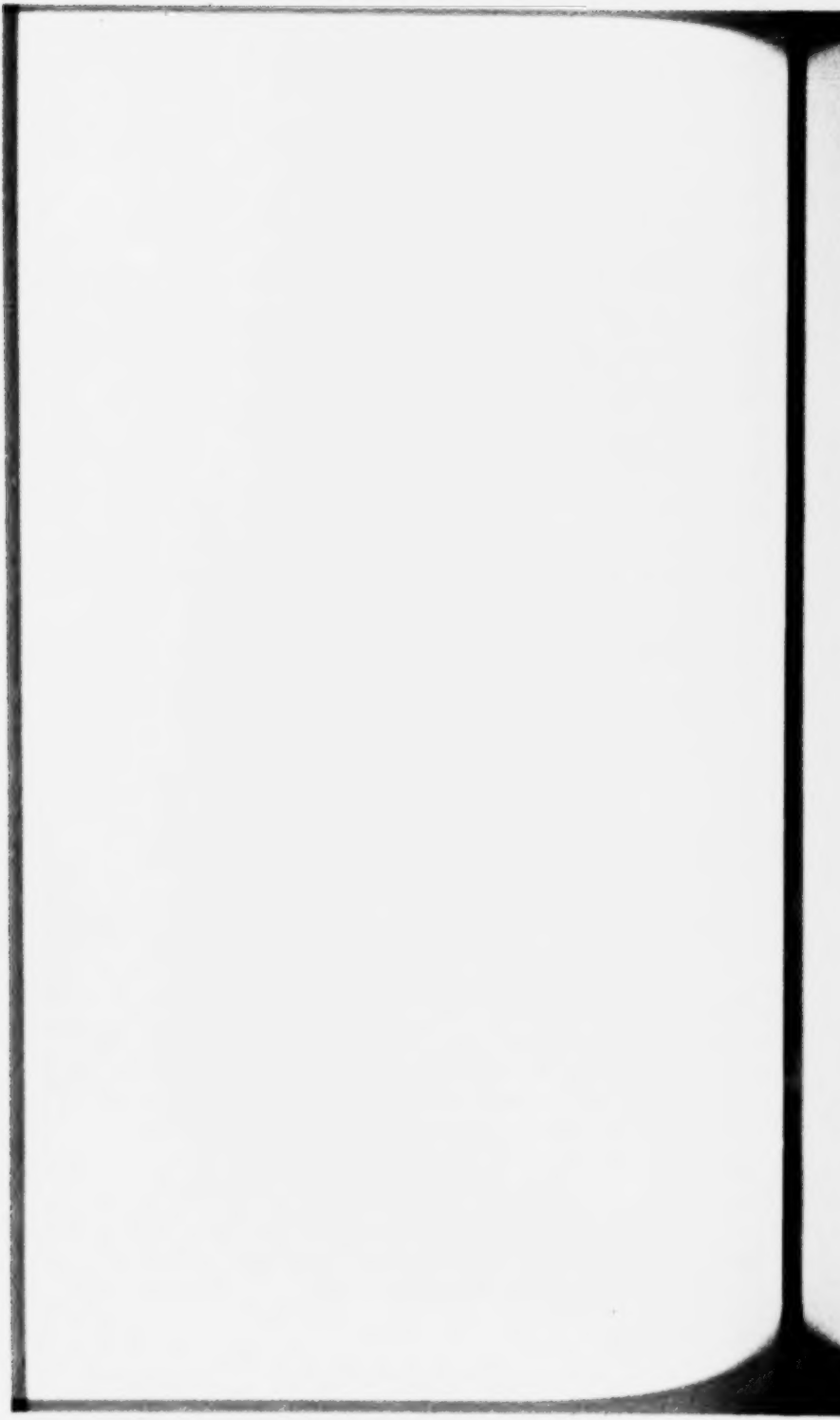
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APPENDIX A

Opinion of the United States Court of Appeals, For the Fourth Circuit

No. 12,200

CARTER-WALLACE, INC.,

Petitioner,

—versus—

JOHN W. GARDNER, Secretary of Health, Education, and Welfare, and JAMES L. GODDARD, Commissioner of Food and Drugs,

Respondents.

ON PETITION TO REVIEW AND SET ASIDE ORDER OF THE COMMISSIONER OF FOOD AND DRUGS.

(Argued October 31, 1968. Decided November 4, 1969)

Before HAYNSWORTH, *Chief Judge,* BUTZNER, *Circuit Judge,* and HUTCHESON, *Senior District Judge.**

Stephen R. Lang (William L. Hanaway; Breed, Abbott & Morgan; Ralph H. Ferrell, Jr., and Hunton, Williams, Gay, Powell & Gibson on brief) for petitioner; and William W. Goodrich, Assistant General Counsel, Department of Health, Education, and Welfare (Joanne S. Sisk and Eugene M. Pfeifer, Attorneys, Department of Health, Education, and Welfare; and Fred M. Vinson, Jr., Assistant Attorney General, and William E. Ryan, Attorney, Department of Justice, on brief) for respondents.

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* Judge Hutcheson participated in the hearing and the decision of this case, but he died before the opinion was completed.

Opinion of the United States Court of Appeals, For the Fourth Circuit

BUTZNER, *Circuit Judge*:

The Commissioner of Food and Drugs subjected meprobamate and compounds containing meprobamate in combination with other drugs to special controls under the Federal Food, Drug & Cosmetic Act.[1] Carter-Wallace, Inc., a manufacturer and distributor of the drug, petitioned for review under the statutory proceedings authorized by the Act and the general provisions of the Administrative Procedure Act.[2] We affirm the Commissioner's order because we believe that his decision is supported by substantial evidence and that it is warranted by law.

I.

In 1965, Congress amended the Federal Food, Drug & Cosmetic Act to provide control over barbiturates, amphetamines, and other drugs having a similar effect on the central nervous system.[3] These drugs were classified as "depressant or stimulant drugs." Control over them is accomplished through increased record keeping and inspection requirements, regulation of intrastate traffic, and by making possession of the drugs, other than by the user, illegal outside of the legitimate channels of commerce. A prescription for a depressant or stimulant drug may not be filled more than six months after the date on which it was issued and it may not be refilled more than five times unless renewed by the prescribing physician.[4]

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[1] 21 U.S.C. §§ 301 et seq.

[2] 21 U.S.C. §§ 321(v), 371(f), and 5 U.S.C. §§ 702, 704, and 706.

[3] H. R. Rep. No. 130, 89th Cong., 1st Sess. 1 (1965).

[4] 21 U.S.C. § 360a; H. R. Rep. No. 130, 89th Cong., 1st Sess. 1, 3 (1965).

Opinion of the United States Court of Appeals, For the Fourth Circuit

The genesis of these proceedings is § 201(v) of the amendments [21 U.S.C. § 321(v)], which provides in part:

> "The term 'depressant or stimulant drug' means—
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> "(1) any drug which contains any quantity of (A) barbituric acid . . .
>
> "(2) any drug which contains any quantity of (A) amphetamine . . .
>
> "(3) any drug which contains any quantity of a substance which the Secretary, after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system. . . ."

The legislative history of this section clearly reflects the concern with which Congress viewed meprobamate. The House Committee Report states:[5]

> "The committee considered the advisability of specifically designating meprobamate [and five other drugs] as 'depressant or stimulant drugs.' It was decided that this should not be done because the Secretary of Health, Education, and Welfare will, under the provisions of proposed section 201(v)(3) of the Federal Food, Drug, and Cosmetic Act, consider designating these drugs as 'depressant or stimulant drugs' and that it would be inadvisable to single out these drugs while leaving out others having substantially similar abuse potentials. The committee expects the Secretary to take early action with respect to the consideration of the listing of these six drugs."

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[5] H. R. Rep. No. 130, 89th Cong., 1st Sess. 13 (1965).

Against this background, the Food and Drug Administration conducted extensive hearings that culminated in subjecting meprobamate to control as a depressant drug. In canvassing the record upon review. we are required to give conclusive effect to the Commissioner's findings of fact that are supported by substantial evidence. 21 U.S.C. § 371(f).[6]

Meprobamate is one of a group of drugs known as minor tranquilizers which are used for the symptomatic relief of anxiety and tension associated with psychoneurotic disorders. It was first used in clinical trials in 1952, and it has been widely distributed commercially since 1955 in tablets or capsules of 200 and 400 milligram doses. Carter-Wallace has produced enough of the drug to make approximately 14 billion tablets. It may be dispensed only by prescription, and an estimated 500 million prescriptions have been written. The maximum recommended adult dosage is 2,400 milligrams daily. Meprobamate is a safe, effective drug when it is taken in accordance with the manufacturer's recommendation under a physician's direction.

In order to subject meprobamate to the Act's special controls the Commissioner must find, first, that it has a depressant effect on the central nervous system; second, that it has a potential for abuse; and, third, that this potential results from its depressant effect on the central nervous system.

There can be no doubt about the sufficiency of the proof of the first element. The regulations [21 C.F.R. § 166.2]

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[6] "Substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." Consolidated Edison Co. v. NLRB, 305 U.S. 197, 229 (1938).

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provide that a drug has a depressant effect on the central nervous system if there is substantial evidence that the drug may produce (a) a calming effect or relief of emotional tension or anxiety; or (b) drowsiness, sedation, sleep, stupor, coma, or general anesthesia; or (c) mood depression or apathy. Nearly all of the medical witnesses testified that the major therapeutic effects of meprobamate are to calm the patient and to give relief from emotional tension or anxiety. A number of witnesses established that large dosages of meprobamate cause stupor and induce apathy. The precise way in which meprobamate achieves these effects is not known with certainty, but the undisputed evidence establishes that it acts upon the central nervous system.

In selecting "potential for abuse" as one of the criteria for subjecting a drug to special control, the House Committee did not intend this to be determined on the basis of the drug's having only a potential for isolated or occasional nontherapeutic purposes. Instead, the committee recommended that a drug's potential for abuse should be determined "on the basis of its having been demonstrated to have such depressant or stimulant effect on the central nervous system as to make it reasonable to assume that there is a substantial potential for the occurrence of significant diversions from legitimate drug channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or the safety of the community."[7]

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[7] H. R. Rep. No. 130, 89th Cong., 1st Sess. 7 (1965). The source of the committee's definition is The President's Advisory Commission on Narcotic and Drug Abuse, Final Report, p. 2 (1963), which states:

"When this report speaks of 'drug addiction' it is using the term in its full technical sense to include both the psycho-

The evidence on this issue is in sharp conflict. It ranges from testimony of Carter-Wallace's experts that the potential for abuse of candy or aspirin is greater than for meprobamate to testimony from a government witness that he became so uneasy about alcoholics' affinity for the drug he stopped prescribing it for them. A number of well-qualified medical witnesses called by Carter-Wallace testified that while treating patients with meprobamate over a period of years they had observed no evidence of the drug's abuse, or at the most they had seen only isolated or occasional cases.

Doctors testifying for the government presented a different picture. They told of patients who used meprobamate to the extent that they became intoxicated—with staggering gait, slurred speech, and impaired coordination. Testimony also disclosed that some persons who took excessive doses of meprobamate felt "high" or experienced euphoria. Credible evidence established that continuous use of the drug produces tolerance to its effects.

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logical and the physical dependence. When it speaks of 'drug abuse' it is referring to the broader problem which includes also those drugs which create only psychological dependency. We will use the term 'drug abuse' in this report as existing when an individual takes psychotoxic drugs under any of the following circumstances:

"(a) in amounts sufficient to create a hazard to his own health or to the safety of the community; or

"(b) when he obtains drugs through illicit channels; or

"(c) when he takes drugs on his own initiative rather than on the basis of professional advice.

"Drug abuse today involves not only the narcotic drugs and marihuana, but to an increasingly alarming extent other drugs such as the barbiturates, the amphetamines and even certain of the 'tranquilizers'. This latter group will be referred to in this report as the 'dangerous drugs'."

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This, in turn, requires more of the drug to achieve the original effect. Excessive use of meprobamate creates physical dependence upon the drug. Its withdrawal from persons who use it to excess may be followed by nausea, insomnia, muscle tremors, and anxiety.

Although complete statistics on the type of drugs used for suicide and attempted suicide by poison are not available, the evidence indicated that meprobamate had been used alone or in conjunction with other drugs in a number of cases. Several drugs are used more frequently than meprobamate for successful suicides. But one qualified researcher observed that meprobamate's use in attempted suicides was surpassed only by barbiturates.

The hearings disclosed significant diversion of meprobamate from legitimate trade. During the 1956-1966 decade, the Food and Drug Administration recorded 1,515 convictions for illegal sales of prescription drugs. Of these, 173 or approximately 11% involved meprobamate. Evidence also exposed how easily the drug can be illegally purchased.

The legislative history reveals that when the phrase "potential for abuse" was adopted, the House Committee rejected the suggestion that special controls should be limited "to those drugs as to which substantial abuse had been shown." The Committee Report emphasizes that the Commissioner should not be required to wait "until a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to controls. . . ."[8] Thus, the existence of abuse is relevant to forecast future abuse, but the incidence of present abuse is not the test which the Commissioner must apply. Instead, he has been charged with the responsibility of

[8] H. R. Rep. No. 130, 89th Cong., 1st Sess. 7 (1965).

assaying future or potential abuse. As might be expected, witnesses differed as much in their opinions about the future as they had concerning their observations of the present. However, a number of qualified experts expressed the view that as access to barbiturates was limited by controls, the abuse of meprobamate would increase unless it also was controlled. Barbiturates and meprobamate can suppress or relieve the withdrawal reaction that an excessive user of alcohol suffers when he is abruptly deprived of his intoxicant. Although most drug-prone alcoholics seek barbiturates, a significant number take meprobamate. The magnitude of the problem was illustrated by the testimony of a knowledgeable witness who expressed the opinion that of the six million alcoholics in the country, approximately four per cent (240,000) would abuse meprobamate if they had free access to it. As an additional indicia of potential abuse, a well-informed student of suicides made "a sophisticated guess" that use of meprobamate as a suicidal agent will increase.

Our examination of the record as a whole leads us to conclude that meprobamate does have a potential for abuse within the meaning of the drug abuse control amendments to the Act.

The third element for subjecting meprobamate to special control is proof that its potential for abuse results from its depressant effect on the central nervous system. Carter-Wallace complains that the government improperly relied upon a presumption created by regulation to prove this point.[9] In its brief the government disclaims any

[9] The regulation follows the President's Advisory Commission on Narcotics and Drug Abuse, Final Report, p. 2 (1963), n. 7 *supra*. The regulation [21 C.F.R. § 166.2(e)] states in part:

"(e) The Commissioner may determine that a substance has a potential for abuse because of its depressant or stimulant

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reliance on the regulation to prove a causal relationship. It contends that the regulation was intended, and used, to list the criteria for establishing a drug's potential for abuse. The regulation is not a model of clarity, and we agree with Carter-Wallace that it cannot be used to dispense with proof of the causal relationship required by the statute. *Miller* v. *United States*, 294 U.S. 435, 440 (1935). However, our review of the record satisfies us that the government's case does not rest on a presumption. In the initial stages of the proceedings neither party placed great emphasis on this requirement of the statute, and the hearing examiner's proposed findings do not refer to it. However, the Commissioner, after hearing oral argument, remedied the hearing examiner's omission by including a new finding on this issue which states:

> "The substantial evidence of record establishes that meprobamate has a potential for abuse, as manifested in the ways set forth in findings 8 through 27 above, because of its depressant effect on the central nervous system. Many of these abuses of meprobamate result from the phenomenon of tolerance to the drug and

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effect on the central nervous system or its hallucinogenic effect if:

"(1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or

"(2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or

"(3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice . . . ."

> the phenomenon of withdrawal reactions upon discontinuance after long-continued or excess use. These phenomena of tolerance and withdrawal reactions are a result of meprobamate's central nervous system depressant effect. Other abuses of meprobamate stem from its euphoric effect which is a function of meprobamate's central nervous system depressant effect. In short, meprobamate's potential for abuse results from its effect of depression on the central nervous system."

Carter-Wallace, asserting this finding is not supported by substantial evidence, takes the position that there is no connection between the depressant effect of any drug and its potential to affect the health of an individual or the safety of the community.[10]

It is true that the finding is not supported by direct evidence. The present state of medical knowledge does not enable anyone to describe with certainty the means by which depressant drugs produce their effects.

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[10] Dr. Frank M. Berger, who is president of Wallace Laboratories, a wholly-owned subsidiary of Carter-Wallace, Inc., testified:

> Q. "Dr. Berger, in your opinion does Meprobamate when taken at recommended doses have such a depressant effect on the central nervous system as to make it reasonable to assume the drug has substantial capability of creating hazards to the health of the user or the safety of the community?"
> A. "I do not think that there is any connection between the depressant effect of Meprobamate or for that matter any other drug and its potential or capability to affect the health of an individual or of the community.
> "This is a very broad statement, a very broad question.
> "Health of an individual is affected if a drug is abused, if it is taken to excess. I have previously mentioned it is exceedingly rare to abuse Meprobamate. The number of individuals who have abused it is very small. As I previously mentioned, the only type of person who will abuse it is a psychopathic individual."

Moreover, eminent scientists espouse different theories to explain effects of central nervous system depressants. Carter-Wallace's witnesses advanced the theory that therapeutic doses of meprobamate act as a depressant on the sub-cortical region of the central nervous system, specifically the interneurons. In this manner it selectively blocks or interrupts circulation of anxiety producing stimuli without affecting the cortical region of the brain. Lack of effect on the cortex precludes the feeling of well-being or euphoria that in other drugs leads to addiction. Excessive doses of meprobamate may affect the cortex, but the theory postulates that by the time the cortex becomes involved, the effect upon the subcortical regions produces stupor and thus precludes a feeling of well-being. In contrast, the theory continues, barbiturates and alcohol have a disinhibiting effect on the cortex, which is the seat of reason. Disinhibition produces a sense of well-being, the kind of kick that calls for repetition and abuse.

Proponents of this theory assert that meprobamate's suppression of withdrawal symptoms from barbiturates and alcohol is irrelevant to the case. They believe physical dependence on a drug, and its consequent withdrawal symptoms, result from the drug's incorporation into and subsequent withdrawal from a cell. Under this theory, physical dependence and withdrawal symptoms have nothing to do with central nervous system depression.

Carter-Wallace's witnesses generally expressed opinions approving of this theory. Without exception, they saw no relation between meprobamate's potential for abuse and its depressant effect on the central nervous system. They explained meprobamate abuse by attributing it to people, not the drug. Only persons who are prone to be

dependent on drugs, not normal persons, will abuse it, their argument runs. The difficulty with this thesis is that while it defines the problem, it does not provide an answer. The record describes many types of people who may become dependent on drugs—including alcoholics, they are legion. But the record does not explain the basic psychological and physiological reasons that cause a person to abuse drugs. This is not unexpected, because present medical knowledge has no definitive explanation. We cannot, however, attribute ignorance of this situation to Congress. It knew that "[w]e lack considerable knowledge of drug abuse and how to treat it."[11] But nothing in the legislative history suggests that a drug is to escape coverage because it attracts only drug-prone people. The Commissioner's refusal to accept Carter-Wallace's thesis was not arbitrary or capricious, although the sincerity of its advocates is unquestioned.

Though the record contains no direct evidence or verified theories to explain meprobamate's effect, the Commissioner's order does not lack evidentiary support. Circumstantial evidence, or indirect proof, can satisfy the requirement that an administrative order be undergirded by substantial evidence. *Dubin-Haskell Lining Corp.* v. *NLRB*, 375 F.2d 568, 573 (4th Cir. 1967), *cert. denied*, 393 U.S. 824 (1968).

It is undisputed that the body's tolerance to alcohol and barbiturates can lead to excessive use of these drugs, which in turn can cause physical dependence on them. Physical dependence may become so great that abrupt deprivation of either barbiturates or alcohol will cause

[11] The President's Advisory Commission on Narcotic and Drug Abuse, Final Report, p. 75 (1963).

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withdrawal symptoms. These symtoms can be suppressed or alleviated by readministering the drug. Moreover, physical dependence and withdrawal symptoms of barbiturates and alcohol are so similar that the withdrawal symptoms of alcohol may be suppressed by administering barbiturates.

Excessive use of meprobamate can cause physical dependence and withdrawal symptoms similar to those caused by barbiturates and alcohol. More significant than mere similarity, however, is the fact that meprobamate can suppress withdrawal symptoms of both alcohol and barbiturates.

A well-qualified witness testifying for the government advanced a theory to explain physical dependence on barbiturates that differed considerably from the cellular incorporation theory urged by Carter-Wallace. The government's witness testified that his research led him to believe that barbiturates have their primary site of action in the sub-cortical region, and from his studies he drew the inference that physical dependence on barbiturates seems to be primarily the result of adapted changes in the subcortical region alone. Other evidence tended to corroborate this theory. The witness accepted the findings that the primary site of action of meprobamate was in the subcortical region of the central nervous system. Emphasizing that his theory of barbiturate dependence had not yet been verified, he suggested that if it is valid for barbiturates, it may be equally valid for meprobamate.

Another comparison of meprobamate, barbiturates, and alcohol supports the Commissioner. The precise reason why some drugs cause euphoria is unknown.[12] However,

[12] Euphoria is defined as "a feeling of well-being or elation, especially one that is groundless, disproportionate to its cause, or

credible evidence indicates that excessive use of barbiturates or alcohol can cause euphoria by depressing the central nervous system. Whether the primary site of their action is the cortex or sub-cortex is a matter of dispute, but for the purposes of this comparison the exact site is not decisive since both the cortical and sub-cortical regions are parts of the central nervous system. Substantial evidence also established that excessive use of meprobamate can cause euphoria. Euphoria can also be caused by stimulant drugs such as amphetamines. However, no evidence was introduced that euphoria results from any effect other than the action of depressant or stimulant drugs on the central nervous system.

We conclude that although the evidence is largely circumstantial, it substantially supports the Commissioner's findings that tolerance, withdrawal reactions, and euphoria are a result of meprobamate's central nervous system depressant effects. Physical dependence (as manifested by withdrawal symptoms and tolerance) and euphoria are among the characteristics of a drug that lead to its abuse. Therefore, taking into account our imperfect knowledge of how drugs injure people, we hold that substantial evidence supports the Commissioner's finding of a causal relation between meprobamate's depressent effect upon the central nervous system and its potential for abuse.

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inappropriate to one's life situation." Webster's Third New International Dictionary (unabridged 1964). Witnesses described euphoria as a state of artificial happiness or elation of mood; or, an abnormal state of well-being, quite different in quality and intensity from a healthy state of well-being.

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II.

Carter-Wallace manufactures five drugs containing meprobamate combined with other substances. It asserts that the combination drugs should not have been included in the Commissioner's order because the examiner reported there was a lack of substantial evidence that they have a substantial potential for significant abuse. Carter-Wallace's position, however, is not supported by the Act. Title 21 U.S.C. § 321(v)(3) provides that the term depressant drug means a drug which contains any quantity of a substance that has a potential for abuse because of its depressant effect on the central nervous system. Since the combination drugs contain meprobamate, a substance satisfying the definition of a depressant drug, they are covered by the plain language of the Act. The Court emphasized in *United States* v. *Dotterweich*, 320 U.S. 277, 280 (1943), that the Act touches the lives and health of people, and it should not be narrowly construed. Certainly we see no reason for excluding drugs that are literally encompassed by its terms.

An exemption from coverage of combination drugs is provided by 21 U.S.C. § 360a(f)(2), which states in part:

> "(2) The Secretary shall by regulation exempt any depressant or stimulant drug from the application of this section, if—
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> . . . . .
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> "(B) he finds that such drug includes one or more substances not having a depressant or stimulant effect on the central nervous system . . . and such substance or substances are present therein in such combination, quantity, proportion, or concentration as to prevent

> the substance or substances therein which do have such an effect from being ingested or absorbed in sufficient amounts or concentrations as, within the meaning of section 321(v) of this title, to—
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> . . . . .
>
> "(ii) have a potential for abuse because of their depressant or stimulant effect on the central nervous system. . . ."

In this hearing the government was required to show only that meprobamate satisfied the Act's definition of a depressant drug and that the combination drugs contained meprobamate. Lack of evidence concerning the effect of the combination drugs cannot be substituted for the affirmative findings required for exemption. Proceedings for exemption may be initiated by the Commissioner or by Carter-Wallace. 21 C.F.R. § 166.7 (1968). Neither the Commissioner's order nor our affirmance precludes prompt action to determine whether the combination drugs should be exempted.

III.

Carter-Wallace alleges that a number of the trial examiner's rulings deprived it of a fair hearing. At a pretrial conference a week before the hearing, the government indicated that it would use documents aggregating 2,550 pages. Carter-Wallace complains that the hearing examiner denied its motion for a continuance of an additional week to allow time for examination of the government's documents. The grant or denial of continuances lies within the sound discretion of a hearing examiner, *NLRB* v. *Siris Products Corp.*, 186 F.2d 503 (4th Cir. 1951), and we find

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no abuse of discretion here. Carter-Wallace had six months to prepare its case, and many of the documents proffered by the government came from Carter-Wallace's own files. The hearings lasted for nearly three months, and during that time Carter-Wallace had ample opportunity to examine the documents. Moreover, it has shown no specific instances of how its lack of opportunity to study the documents for an additional week before the hearing prejudiced its case.

Carter-Wallace objected to government exhibit 202, which is a summary purporting to show, among other things, that an audit of 99 pharmacies disclosed a shortage of 796,000 tablets of meprobamate. The shortage represented 77% of the total amount of the drug received by the pharmacies in a one-year period. The witness through whom the summary was introduced was not familiar with all of the underlying data, and some of the underlying documents were not available for use in cross-examination. While hearsay evidence is generally admissible in an administrative hearing, we think the deficiencies concerning the underlying data made it difficult for the government to establish the reliability of its audit and precluded meaningful cross-examination by Carter-Wallace. See *McDaniel* v. *United States*, 343 F.2d 785, 789 (5th Cir.), *cert. denied*, 382 U.S. 826 (1965). *In Re Shelley Furniture*, 283 F.2d 540, 543 (7th Cir. 1960).

However, other evidence supports the finding that there has been a significant diversion of meprobamate from legitimate channels. Furthermore, proof of the drug's potential for abuse does not rest solely upon showing its diversion. Other findings, amply supported, suffice to establish that meprobamate has a potential for abuse. Intro-

duction of exhibit 202, therefore, is not cause for setting aside the Commissioner's order. *Willapoint Oysters, Inc.* v. *Ewing*, 174 F.2d 676, 690 (9th Cir.), *cert. denied*, 338 U.S. 860 (1949).

Carter-Wallace's complaint about the introduction of other hearsay on the ground that it was denied its right of cross-examination is without merit. Over Carter-Wallace's objection, the examiner permitted a physician employed by the Food and Drug Administration to introduce records showing adverse effects of meprobamate. Carter-Wallace complained that the doctors and hospital officials who reported the cases were not available for cross-examination and that the witness could not attest to the accuracy of the records by her own personal knowledge. The records, however, had been furnished the Food and Drug Administration by Carter-Wallace in accordance with a manufacturer's duty to report adverse reaction in connection with new drug applications. Thus Carter-Wallace had ample opportunity to investigate the accuracy of the reports. Indeed, considering the nature of the reports, it is unlikely that it did not do so. Other documents admitted over Carter-Wallace's objection were articles concerning meprobamate published in recognized scientific journals. Carter-Wallace, of course, had full opportunity to examine the government's expert witness on her opinion of the validity of the scientific opinions that were expressed. We find no abuse of the examiner's discretion in the admission of these exhibits. *Rocker* v. *Celebrezze*, 358 F.2d 119, 122 (2d Cir. 1966); *Montana Power Co.* v. *Federal Power Comm.*, 185 F.2d 491, 498 (D.C. Cir. 1950), *cert. denied*, 340 U.S. 947 (1951).

Carter-Wallace complains that in contrast to the examiner's admission of scientific papers offered by the govern-

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ment, a pertinent paper which it sought to introduce was excluded. This unpublished paper was of recent origin. Its author had conferred with Carter-Wallace's attorneys in the town where the hearings were held the night before the session at which the paper was submitted. Carter-Wallace, however, did not call the author as a witness, but instead sought to introduce the paper through its vice-president. Under these unusual circumstances, the examiner did not abuse his discretion by ruling that the paper could not be introduced unless the government had an opportunity to cross-examine the author.

We agree with Carter-Wallace that the examiner erroneously ruled that three papers written by the president of Wallace Laboratories, were irrelevant. However, the author testified at great length, and the exhibits were largely cumulative. Their exclusion was not reversible error. Cf. *United States* v. *Ross Corporation,* 385 F.2d 564, 566 (6th Cir. 1967). See 2 Davis, *Administrative Law* § 14.09, p. 291 (1958). Carter-Wallace's contention that the examiner was biased is not supported by the record. We find no merit in its other complaints about the conduct of the hearing or in its charge that the examiner and the Commissioner ignored its evidence.

The order of the Commissioner is affirmed.

APPENDIX B

Opinion of the FDA Hearing Examiner, Dated January 13, 1967

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

Docket No. FDA-DAC-1

This administrative proceeding involves the basic question of whether or not the drug Meprobamate, and drugs containing Meprobamate, have sufficient potential for abuse because of their depressant effect on the central nervous system to warrant bringing them under the control of the Drug Abuse Control Amendments of 1965. This is the first administrative proceeding to be conducted under these most recent amendments to the Federal Food, Drug, and Cosmetic Act of 1938.

In July of 1965, the Congress unanimously passed the Drug Abuse Control Amendments of 1965[1] to the Federal Food, Drug, and Cosmetic Act.[2] These Amendments, among other things, legislatively brought under more strict control the manufacture, sale and distribution of specifically identified "depressant or stimulant drugs." Thus, one class of depressant drugs, the so-called barbiturate drugs, and another class of stimulant drugs, the so-called amphetamine drugs were specifically named in this legislation and brought under its control. [21 U.S.C. 201(v); 21 U.S.C. 360 and 360a; 79 Stat 227, 231, 232, and 228].

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[1] P.L. 89-74, July 15, 1965, hereinafter referred to as the "Amendments."

[2] 21 U.S.C. 321 et seq., hereinafter referred to as the "Act."

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Opinion of the FDA Hearing Examiner, Dated January 13, 1967

What other "depressant or stimulant" drugs are to be controlled under these Amendments, if any, was left for Administrative determination.[3] Section 201(v)(3) of the Act, [21 U.S.C. 321(v)(3)] defines the term "depressant or stimulant" drugs to mean—

> (3) "any drug which contains any quantity of a substance which the Secretary, after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system * * *"

The administrative process to be followed to arrive at this determination was made subject to the public hearing and appeal procedures set forth in the basic Federal Food, Drug, and Cosmetic Act. [21 U.S.C. 321, 371].

Pursuant to the authority set forth in those Amendments and delegated to the Commissioner of Food and Drugs [21 CFR 2.90], the Acting Commissioner of Food and Drugs on January 18, 1966, caused to be published in the FEDERAL REGISTER a proposal to designate all drugs containing any amount of 17 named substances as having a potential for abuse because of their depressant or stimulant effect on the central nervous system or their hallucinogenic effect. These drugs would thus be subject to the controls of the Amendments. [Ex. A; 31 F.R. 565].

One of the drugs proposed for control, bears the established name of "Meprobamate" and various and numerous trade names, the most popular of which are Miltown and Equanil. This proposal was published pursuant to the statutory provisions of the Act and invited all interested

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[3] C. Ex. 2, p. 5, "Scope of Coverage."

persons to submit their views in writing regarding this proposal. [21 U.S.C. 371(e)].

On March 19, 1966, the Commissioner of Food and Drugs caused to be published in the FEDERAL REGISTER an Order by which 16 of the proposed 17 drugs were designated as being brought under control of the Amendments. Meprobamate and all drugs containing any amount of Meprobamate were designated in this Order as having a potential for abuse because of their "depressant effect on the central nervous system." [Ex. B; 31 F.R. 4679].

Wallace Laboratories, a division of Carter-Wallace, Inc., of Cranbury, New Jersey [hereinafter referred to as Respondent], a pharmaceutical firm engaged in the manufacture, sale, and distribution of Meprobamate, through its attorneys, filed timely objections to the Commissioner's Order of March 19, 1966, as it related to Meprobamate, and requested a hearing on its objections.

Pursuant to statutory provisions there was published in the FEDERAL REGISTER of May 17, 1966, a combined Notice and Order which, among other things, noted the filing of objections by Respondent and stayed those provisions of the Order of March 19, 1966, relating to Meprobamate. This document further set forth four numbered issues which were raised by the filing of objections to the March 19, 1966 Order and announced the time and place for a prehearing conference and hearing concerning Meprobamate. [Ex. C; 31 F.R. 7174]. Three of the four numbered issues set forth in this document concern Meprobamate, the fourth concerns other drugs not the subject of these proceedings.

In order to expedite the hearing as noted above, and upon Respondent's request, an additional prehearing con-

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ference was scheduled by Notice published in the FEDERAL REGISTER of May 26, 1966. [Ex. D; 31 F.R. 7573].

Two prehearing conferences were held in this matter, the first on June 14, the second on June 21, 1966. The issues upon which evidence would be taken during the hearing, and as they related specifically to Meprobamate, were particularized during these conferences as follows:

1. Whether there is evidence that individuals are taking Meprobamate, or drugs containing Meprobamate, in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community?
2. Whether there is evidence of significant diversion of Meprobamate, or drugs containing Meprobamate, from legitimate drug channels?
3. Whether there is evidence that individuals are taking Meprobmate, or drugs containing Meprobamate, on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice? [Ex. C; PH. TR. 8, 12, and 13].[4]

During these prehearing conferences, Respondent's counsel objected to the wording of issues numbered one and three, *supra.*

The grounds for the objections are that the issues establish a burden of proof not consistent with the Amend-

[4] PH. TR.—refers to pages of transcript of the prehearing conferences. TR.—refers to pages of the transcript of the hearing. G. Ex.—abbreviation for Government's exhibits. R. Ex.—abbreviation for Respondent's exhibits.

ments and their legislative history and therefore are in excess of statutory authority.

It is Respondent's position that as worded, issues numbered one and three would allow the Food and Drug Administration to list Meprobamate as a drug subject to control under the Amendments upon proof of only a few individuals having taken the drug in amounts hazardous to their health or upon proof that only a few individuals have taken the drug on their own initiative rather than pursuant to a doctor's prescription.

In short, Respondent contends that Congress intended to demand proof of "substantial" potential for "significant" abuse to warrant bringing a drug under the control of the Amendments. The legislative history of the Amendments are relied upon to support this contention.[5]

In order to answer the three issues as stated in the Notice of Hearing with any degree of certainty, it becomes necessary to first answer the legal question raised by Respondent, namely, what quantum of proof is required under the Amendments to justify the listing of a drug as having a potential for abuse because of its depressant effect on the central nervous system.

Because this matter is one of first impression under the Amendments and the consequent lack of judicial precedent, it may be helpful to trace the origin of the concepts embodied in the issues as stated in the Notice of Hearing, Exhibit C.

On January 27, 1966, the Commissioner of Food and Drugs, pursuant to Sections 201(v), 511, and 701 of the Act [21 U.S.C. 321(v), 360a, and 371] published in the

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[5] PH. TR. 7-14, 167-177; R. Exs. 65 and 66 for identification; Respondent's brief, Part IA.

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FEDERAL REGISTER regulations supplementing, interpreting, and establishing procedures under the Amendments [31 F.R. 1271; 21 C.F.R., 166.1 et seq]. Paragraph 166.2 of these regulations established "Criteria applicable to terms used or defined in paragraph 166.1" of these regulations, which paragraph set forth definitions and interpretations of terms used in the Amendments.

Subparagraphs (a), (b), (c), and (d) of paragraph 166.2 of these regulations, set forth criteria which, among other relevant factors, the Commissioner will consider in determining whether any given drug has a "stimulant effect" (a); a "depressant effect" (b); is "habit forming" (c); or has a "hallucinogenic effect" (d).

Subparagraph (e), most applicable to the question now before us, reads as follows:

> (e) The Commissioner may determine that a substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect, if:
>
> (1) There is evidence that individuals are taking the drug or drugs containing such substances in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or
>
> (2) There is significant diversion of the drug or drugs containing such substances from legitimate drug channels; or
>
> (3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to admin-

ister such drugs in the course of his professional practice;—

• • •

A reading of Exhibit C, the Notice of Hearing in this matter, reveals that the issues for hearing therein stated are framed substantially verbatim in the words of subparagraph 166.2(e) above quoted.

One of the important and basic documents in the legislative history of the Amendments of 1965 is the Final Report of the President's Advisory Commission on Narcotics and Drug Abuse, dated November 1963. [G. Ex. 1]. The concepts set forth in paragraph 166.2 of the regulations referred to above and refined into the issues for the hearing in this matter are first clearly set forth in this Final Report where, at page 2, the following appears:

"When this report speaks of 'drug addiction' it is using the term in its full technical sense to include both the psychological and the physical dependence. When it speaks of 'drug abuse' it is referring to the broader problem which includes also those drugs which create only psychological dependence. We will use the term 'drug abuse' in this report as existing when an individual takes psychotoxic drugs under any of the following circumstances:

(a) in amounts sufficient to create a hazard to his own health or to the safety of the community; or

(b) when he obtains drugs through "illicit" channels; or

(c) when he takes drugs on his own initiative rather than on the basis of professional advice.

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Drug abuse today involves not only narcotic drugs and marihuana, but to an increasingly alarming extent other drugs such as barbiturates, the amphetamines, and even certain of the 'tranquilizers.' This latter group will be referred to in this report as the 'dangerous drugs'."

The above-quoted concepts were incorporated into the formal legislative history of the Amendments in the Report of the Committee on Interstate and Foreign Commerce on H.R. 2. [House Report No. 130, 89th Cong., 1st sess., March 2, 1965; C. Ex. 2]. At page 7, the following section entitled "Potential for Abuse" appears:

The bill provides that the term "depressant or stimulant drug" includes, in addition to barbiturates and amphetamines, any drug which contains any quantity of a substance which the Secretary, after investigation, " • • • designates as having a potential for abuse • • •." The term "drug abuse" was defined for purposes of the report of the President's Advisory Commission on Narcotic and Drug Abuse, submitted November 1, 1963, as existing when an individual takes drugs under any of the following circumstances:

(a) in amounts sufficient to create a hazard to his own health or to the safety of the community; or

(b) when he obtains drugs through illicit channels; or

(c) when he takes drugs on his own initiative rather than on the basis of professional advice.

It is not intended by the committee that a drug's potential for abuse be determined on the basis of the

drug's having a potential for isolated or occasional nontherapeutic purposes. The committee feels that a drug's "potential for abuse" should be determined on the basis of its having been demonstrated to have such depressant or stimulant effect on the central nervous system as to make it reasonable to assume that there is a substantial potential for the occurrence of significant diversions from legitimate drug channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or the safety of the community.

It was recommended to the committee that the coverage of drugs under this paragraph be limited to those drugs as to which substantial abuse had been shown. The committee felt that the Secretary of Health, Education, and Welfare should not be required to wait until a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to controls of the bill. Similarly, the committee considered but did not adopt an amendment requiring that before a drug can be classified as subject to the controls of the bill, the Secretary must determine that it have a "potential for abuse adversely affecting the public health" since the committee felt that this limiting language was not necessary.

The above-quoted paragraph also appears, substantially verbatim, in the Report of the Committee on Labor and Public Welfare, accompanying H.R. 2, dated June 21, 1965. [Senate Report No. 337, 89th Cong., 1st sess., June 21, 1965; G. Ex. 3].

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An exhaustive review of the legislative history of the Amendments fails to reveal nor has our attention been directed to any additional material bearing directly on the question now under consideration. The answer to our question is thus contained in the House and the Senate Reports accompanying the Amendments, and is arrived at, hopefully, through the application of common sense and the principals [sic] of statutory construction.

> "Legislative language is generally most faithfully construed when it is held to mean simply what it says, read with common sense."

United States v. *Vitamin Industries, Inc., et al.*, 130 F. Supp. 755 (D. Neb., 1955). See also: *National Labor Relations Board* v. *Coca-Cola Bottling Co.*, 350 U. S. 264 (1956).

The two key words involved here are "substantial" and "significant," and the common, ordinary meaning to these words must be used. "Substantial" has been authoritatively defined by many courts, in relation to the phrase "substantial evidence." The widely accepted definition is:

> "more than a mere scintilla"; "sufficient for a reasonable mind to accept as adequate to suport a conclusion."

Consolidated Edison Co. v. *Labor Board*, 305 U. S. 197, 229; *Labor Board* v. *Columbian Enameling and Stamping Co.*, 360 U.S. 292, 300; *Universal Camera Corp. v. National Labor Relations Board*, 340 U. S. 474 (1951); *National Labor Relations Board* v. *Walton Manufacturing Co.*, 369 U. S. 404 (1962).

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"Significant" is commonly understood to mean "meaningful," "having meaning," "important," "deserving of consideration."[6]

When the legislative history set out supra is studied and the above-stated definitions are applied with common sense to our problem, it is clear that Respondent's contention must be sustained. Therefore, the answer to the basic legal question presented here, is, that Congress did intend to demand proof of a "substantial" potential for "significant" abuse to justify bringing a drug under the control of the Amendments.

As a corollary to its basic contention, Respondent also argues that in order to prove potentiality for abuse, evidence must be adduced showing that a "significant" number of individuals have abused Meprobamate. Further, the significance of the number of individuals must be measured by comparing the numbers of individuals who have abused Meprobamate with the number of individuals who have abused those drugs specifically designated by Congress as having a potentiality for abuse and legislatively brought under the control of the Amendments, that is, the barbiturates and amphetamines.

Certainly, in the light of the legislative history present here, evidence of an "isolated or occasional" individual's use of Meprobamate for nontherapeutic use would not be sufficient to prove "significant" abuse. The number of individuals must be "significant," that is, "meaningful," "important," and "deserving of consideration." Thus, this portion of Respondent's corollary argument is correct.

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[6] Webster's Third New International Dictionary, Unabridged, 1961, p. 2116.

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However, we are unable to find, nor are we cited to, any provision either in the Amendments themselves or in their legislative history which indicates any intention of Congress to requre that the evidence establish that any specific or arbitrary number of individuals have abused a drug in the past to support a finding of significant abuse. Indeed, in view of the "in future" nature of the "potentiality for abuse" concept embodied in the Amendments, as commented on next in this Opinion, and because accurate and specific numbers of individuals who have abused drugs is not known and cannot be reasonably ascertained with any reliable degree of certitude as set forth in the Findings of Fact which follow, no such numerical criteria is either feasible or desirable. Additionally, the Amendments and legislative history are equally devoid of any indication that Congress intended the significance of the abuse of a drug under consideration to be measured by comparing the number of individuals who have abused it with the number of individuals who have abused the barbiturates and amphetamines. For the above-stated reasons, such a criteria is equally unfeasible and undesirable. Thus, this portion of Respondent's corollary argument must fail as unsupported by law or logic.

In the Amendments Congress dealt with a "potentiality" for abuse, that is, a "possibility" or a "capacity" not yet realized, or "having the capacity or a strong possibility for development into a state of actuality"—a "state of that which is not yet fully realized."[7]

Thus, there is the concept of *future* attainment or fulfillment inherent in the statutory phrase "potential for abuse."

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[7] Webster's Third New International Dictionary, Unabridged, 1961, p. 1775.

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Consequently, as to *when* a drug may be listed as subject to the controls of the Amendments, it is clear from the last paragraph of the House Report, quoted *supra*, that the Secretary need not wait until "* * * a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to (the) controls of the bill." Indeed, the main purpose of the Amendments is to prevent such destruction of lives and to avoid the creation of abusive drug practices, where possible.

However, in this case, where Meprobamate has been on the market for over ten years, the surest means of establishing a "potential for abuse" is to ascertain whether the drug has been abused in the past.

Thus, under the conclusions set forth in this Opinion, and under applicable law, the quantum of proof necessary in *this* proceeding is substantial evidence establishing that Meprobamate has a substantial potential for significant abuse as shown by the past abuse of this drug.[8]

Consequently, the ultimate questions to be decided here are as follows:

> Is there substantial, probative, and reliable evidence of—
>
> (1) significant use of Meprobamate, or drugs containing Meprobamate, in amounts sufficient to create a hazard to the health of the individual or to the safety of other individuals or the community?
>
> (2) significant diversion of Meprobamate, or drugs containing Meprobamate, from legitimate drug channels?

[8] 21 U.S.C. 371(a)(3).

(3) significant use of Meprobamate, or drugs containing Meprobamate, by individuals on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice?

The substantial, probative, and reliable evidence introduced at the hearing in this matter, and a consideration of the record in its entirety, including all arguments and briefs submitted, leads to the conclusion, as more fully detailed in the Findings and Conclusions hereinafter set forth, that Meprobamate does have a substantial potential for significant abuse because of its depressant effect on the central nervous system, within the meaning of 21 U.S.C. 321(v) (3). It therefore is subject to the provisions of the Drug Abuse Control Amendments of 1965.

The Respondent further argues that there is no evidence of record proving that its products consisting of Meprobamate combined with other drugs; i.e., Milpath, Deprol, Milprem, Miltrate, and Appetrol, have a potential for even isolated or occasional abuse. [R. Brief, pp. 49-51, 60-61].

There is a lack of substantial evidence in this record that Meprobamate combined with other drugs, manufactured by either the Respondent or others, have a substantial potential for significant abuse. However, such evidence is not determinative of the question of whether such combination products should be brought under the control of the Amendments. This question is determined by the clear wording of section 201(v)(3) of the Amendments.

[21 U.S.C. 321(v)(3)]. In pertinent part, this section provides:

> "(v) The term 'depressant or stimulant drug' means—
>
> (3) any drug which contains any quantity of a substance which the Secretary, after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect;—"

Meprobamate, after the investigation here involved, is found to be a substance having a potential for abuse because of its depressant effect on the central nervous system. Based upon this finding, all drugs containing any quantity of Meprobamate are "depressant or stimulant drugs" by operation of law, and as such, are subject to the controls of the Amendments.

It is recommended that the proposed Findings of Fact, Conclusions of Law and Order attached hereto, be adopted by the Commissioner and published in the FEDERAL REGISTER.

Dated: January 13, 1967

WILLIAM E. BRENNAN
Hearing Examiner

APPENDIX C

Findings of Fact and Conclusions of Law of the Commissioner of Food and Drugs, Dated November 28, 1967

Meprobamate; Listing Drug as Subject to Control

In the matter of listing meprobamate as a drug subject to control under the Drug Abuse Control Amendments of 1965:

Acting on a proposal published in the FEDERAL REGISTER of January 18, 1966 (31 F.R. 565), an order was published in the FEDERAL REGISTER of March 19, 1966 (31 F.R. 4679), listing meprobamate, among other drugs, as a drug subject to control under the Federal Food, Drug, and Cosmetic Act as amended by the Drug Abuse Control Amendments of 1965 because of its potential for abuse due to its depressant effect on the central nervous system. Subsequently, Wallace Laboratories, a division of Carter-Wallace, Inc., Cranbury, N.J., filed objections to such listing of meprobamate and requested a public hearing, and it was concluded that the objections stated reasonable grounds.

Accordingly, an order was published in the FEDERAL REGISTER of May 17, 1966 (31 F.R. 7174), that, among other things, stayed the effectiveness of so listing meprobamate and scheduled a public hearing for the purpose of receiving evidence relevant and material to the issues set forth in that order plus a prehearing conference for certain purposes. An additional prehearing conference in this matter was announced in the FEDERAL REGISTER of May 26, 1966 (31 F.R. 7573).

Prehearing conferences were held on June 14 and 21, 1966, and the public hearing began June 27, 1966, and ended September 16, 1966. The transcript of testimony (4,891 pages) sets forth the testimony of 31 witnesses on behalf of

the Government and 31 on behalf of the respondent. Fifty witnesses were medical doctors covering a wide range of medical training, experience, and expertise. On behalf of the Government, 118 exhibits were introduced into evidence, and 24 were introduced by the respondent. Written briefs were timely-filed by the respondent and the Government.

In the FEDERAL REGISTER of April 13, 1967 (32 F.R. 5933), a tentative order including proposed findings of fact and conclusions in this matter was published providing for the filing of exceptions thereto within 30 days by any interested person whose appearance was filed at the hearing. Thereafter, the Commissioner of Food and Drugs considered the exceptions received to the tentative order and listened to oral arguments on behalf of Wallace Laboratories, a division of Carter-Wallace, Inc.

Now, therefore, on the basis of the evidence received at the hearing, and after consideration of the written and oral arguments, proposed findings and conclusions, and exceptions to the tentative order, which are adopted in part or rejected in part as is apparent from the detailed findings herein made, and pursuant to the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 201(v), 511, 701, 52 Stat. 1055, as amended, 79 Stat. 227 et seq.; 21 U.S.C. 321(v), 360a, 371) and delegated by him to the Commissioner (21 CFR 2.120), the following order is issued:

Findings of fact.[1] 1. Meprobamate, N.F., is the "established name" for a white crystalline substance having the

[1] The citations following each finding of fact refer to the pages of the transcript of testimony and the exhibits received in evidence at the hearing, unless specified otherwise. "TR" refers to the transcript, "G. Ex." refers to exhibits on behalf of the Government, and "R. Ex." refers to exhibits introduced by the respondent.

chemical formula 2-methyl-2-*n*-propyl-1,3-propanedial dicarbamate. It is a carbamate compound which was developed by Berger and Ludwig from an earlier developed short-acting tranquilizer named "mephenesin." Meprobamate was first used in clinical trials in 1952 as an antianxiety agent and has been widely distributed commercially since 1955. (TR. 1679-1681; R. Ex. 47.)

2. Meprobamate is one of a group of drugs known collectively as "tranquilizers." It is recommended by its manufacturer and is widely used for the symptomatic relief of anxiety and tension states. It is used in the treatment of tension headaches, nervousness, muscular tension, various complaints related to the gastrointestinal tract, and nervousness and tension associated with psychoneurotic disorders. It is widely used in the treatment of individuals with neurotic personalities and as an adjunct in psychoanalytical therapy. It is also prescribed by some physicians to relieve the anxiety and tension associated with such physical disorders as coronary diseases, pre- and post-operative care, neuromuscular pain, gastrointestinal disorders, menopausal disorders, ear and throat disorders, and alcoholism. Based on its most frequent use, meprobamate is classified as a "minor" tranquilizer in contradistinction to a group of drugs known as "major" tranquilizers. This latter class of tranquilizers is recommended for use in treating the anxiety states associated with psychotic disorders, whereas the "minor" tranquilizers are recommended for use in treating the anxiety states associated with psychoneurotic disorders. (TR. 793, 945, 1680, 1685, 1966-1967, 2015, 2255, 2300, 2935-2936, 3030-3031, 3099, 3187, 3439, 3519, 3613, 3812; R. Ex. 13.)

3. Since its first introduction into the commercial channels of drug distribution in 1955, meprobamate may be

legally dispensed only upon the written prescription of a practitioner licensed by law to administer such drugs, or upon an oral prescription of such practitioner that is reduced promptly to writing and filed by the pharmacist, or by the refilling of any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order that is reduced promptly to writing and filed by the pharmacist (21 U.S.C. 353(b)(1)(B)).

4. Meprobamate is manufactured and distributed by the respondent in these proceedings, Wallace Laboratories, a wholly owned subsidiary of Carter-Wallace, Inc. It is commercially available in two tablet strengths, 200 and 400 milligrams. It is also available in the same strengths in time-release capsule form under the trade name Meprospan. It is most widely marketed by Wallace Laboratories in tablet form under the trade name Miltown. The respondent states that since 1955, it has manufactured approximately 12,500 pounds of meprobamate, which, if all of this material were converted into 400-milligram tablets, would represent approximately 14 billion tablets. It has been estimated that approximately 500 million prescriptions have been written for meprobamate and that it has been prescribed for approximately 100 million patients in the United States. It clearly has been widely distributed in this country for the past 10 years. The usual adult dosage recommended by the respondent is one or two 400-milligram tablets three times daily. The maximum adult dosage recommended is six 400-milligram tablets daily, or 2,400 milligrams of meprobamate. Doses above 2,400 milligrams are not recommended by the respondent. (TR. 1159, 1681-1683, 1751-1752, 1967, 2023, 2036, 2617-2618)

5. The respondent also manufactures and distributes the following drugs in tablet and/or capsule form, which consist of meprobamate combined with other drugs. These drugs have been distributed commercially since the year indicated in the following listing of these products:

Appetrol: Meprobamate plus dextro-amphetamine sulfate; 1959 (1962 in sustained-released form).

Deprol: Meprobamate plus benactyzine hydrochloride; 1958.

Milpath: Meprobmate plus tridihexethyl chloride; 1957.

Milprem: Meprobamate plus conjugated estrogens; 1957.

Miltrate: Meprobamate plus pentaerythrityl tetranitrate; 1958. (Tr. 1750-1754)

6. Meprobamate is a drug having a "depressant effect on the central nervous system" within the meaning of the Drug Abuse Control Amendments and the regulations promulgated thereunder. (21 U.S.C. 201 (v) (3)).

In §166.2 *Criteria applicable to terms used or defined in §166.1* of the depressant and stimulant drug regulations (21 CFR 166.2), "depressant effect" is explained in paragraph (b) in part as follows:

(b) In determining whether a drug has a "depressant effect" on the central nervous system, the Commissioner will consider, among other relevant factors, whether there is substantial evidence that the drug may produce one of the following:

(1) Calming effect or relief of emotional tension or anxiety.

(2) Drowsiness, sedation, sleep, stupor, coma, or general anesthesia.

(3) • • •

(4) Mood depression or apathy.

(5) • • •

Substantially all of the medical witnesses appearing on behalf of both the respondent and the Government, testified in substance that the major pharmacological effects of meprobamate are to calm the individual, to give relief of emotional tension or anxiety, and to produce drowsiness, sedation, and sleep. The unrebutted testimony of a number of witnesses established that meprobamate in sufficiently large dosages produces stupor and coma and will depress mood and induce apathy.

Meprobamate is classified by its developer as, and is represented by the respondent to be, a tranquilizer belonging to the "central depressant" class of tranquilizers.

It is the respondent's position that meprobamate has a potential for only isolated or occasional abuse and that such abuse is not due to its "depressant effect on the central nervous system." (R. Brief 4, 10, 43-49, 53, 54.)

The substantial evidence of record, conclusively establishes that meprobamate acts upon the central nervous system and that such action is a depressant action which results in the calming of individuals who take the drug and the relieving of their anxiety and emotional tension. This drug is known to produce drowsiness, sedation, and sleep. Individuals consuming meprobamate in sufficiently high dosages for extended periods of time have experienced apathy and a depression of mood.

The precise way in which these effects are brought about is the subject of differing medical opinions and views and

is not known with precise certitude. Some medical opinions hold that meprobamate exerts a "selective action" in the central nervous system, affecting primarily the subcortical area of the brain. This causes a blocking of the interneuronal transmission of anxiety-producing electrical discharges or stimuli within the various areas of the brain, the cortex, thalamus, and hypothalamus. It is believed that the site of action of this drug is in the subcortical structures of the brain, such as the thalamus and limbic system. These anatomical structures are thought to be the seat of human emotions; however, it is generally recognized that these structures are part of the central nervous system. When taken not in excess of the maximum recommended dose, meprobamate appears not to significantly affect the functions of the upper area of the brain, the cortex, which is associated with intellectual and judgmental functions, nor the hypothalamus, associated with autonomic functions such as circulation and respiration; however, when meprobamate is taken in dosages higher than those recommended, it does affect the hypothalamus and cortex.

Although the precise mechanism of meprobamate is not known with certainty, nor are there adequate clinical studies clearly delineating its mechanisms, what effects this drug does produce are due to its depressant effect on the central nervous system.

Of those drugs whose principal effect is on the central nervous system, only those with a chiefly depressant effect will, upon sudden withdrawal following chronic administration, produce withdrawal symptoms or an abstinence reaction characterized by insomnia, nausea, vomiting, tremors, the twitching of muscles, anxiety, weakness, headaches, anorexia, unsteady gait or motor ataxia, hallucinations, delusions, depression, convulsions, and, in extreme cases, death.

Carefully controlled clinical studies conclusively establish that when meprobamate is given to individuals in dosages of from 8 to 16 400-milligram tablets daily, for a period of 40 days, and a chemically inert substance, a placebo, is abruptly substituted for the meprobamate, the withdrawal symptoms of insomnia, vomiting, tremors, ataxia, overt anxiety, anorexia, muscle twitching, hallucinations, and convulsions occur. These clinical studies have been confirmed by animal studies.

Other widely recognized central nervous system depressant agents, such as the barbiturates and alcohol, if taken at sufficient dosage levels over sufficient periods of time, will cause withdrawal symptoms when abruptly withdrawn from individuals. On the other hand widely recognized central nervous system stimulant drugs, such as the amphetamines, when suddenly withdrawn from individuals after long use at sufficient dosage levels do not cause withdrawal symptoms.

It is therefore concluded that irrespective of the precise mechanisms of meprobamate, the substantial evidence of record conclusively establishes that this drug does have a "depressant effect on the central nervous system" within the meaning of the amendments. (TR. 39-47, 456-481, 1674-1688, 1705-1706, 1708, 1732, 1851, 2061-2062, 2310, 2350-2353, 2381-2383, 2493-2497, 3027-3028, 3396, 3410, 3677-3678, 4690-4699, 4705-4726, 4748-4762; R. Ex. 10, 11, 13, 19, 33, 44, 47; G. Ex. 1, 12, 17, 19, 24, 28, 150, 162.)

7. Section 166.2(e) of the depressant and stimulant drug regulations (21 CFR 166.2(a)) sets forth the criteria for determining whether a substance has a potential for abuse because of its depressant effect on the central nervous system. Subparagraphs (1), (2), and (3) of §166.2(e) are

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applicable to this proceeding and the criteria are set forth therein, as follows:

(e) The Commissioner may determine that a substance has a potential for abuse because of its depressant * * * effect on the central nervous system * * * if:

(1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or

(2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or

(3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

Respondent argues that Congress intended the Drug Abuse Control amendments to apply only to those substances where there is "demonstrated" a "substantial" potential for "significant" abuse (Part I of respondent's brief). The legislative history of the amendments as set forth in Government Exhibits 1, 2, and 3 does support respondent's argument to the extent that Congress intended to bring under the control of the amendments those substances having a "substantial" potential for "significant" abuse. However, the legislative history does not support the argument that a substance may be brought under the control of the amendments only after substantial abuse has taken place.

The following language appearing at page 5 of the report of the Senate Committee on Labor and Public Welfare

accompanying the amendments, explicitly states: "The Secretary of Health, Education, and Welfare should not be required to wait until a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to controls of the bill." (G. Ex. 3, Sen. Rept. No. 337, 89th Cong., 1st sess., June 21, 1965, p. 5.)

Substantially identical language appears also at page 7 of the report of the House Committee on Interstate and Foreign Commerce accompanying the amendments. (G. Ex. 2, H. Rept. No. 130, 89th Cong., 1st sess., Mar. 2, 1965, p. 7.) Consequently the criterion of "substantial" potential for "significant" abuse has been used in reviewing and evaluating the evidence of record in this matter.

8. The substantial evidence of record establishes that a significant number of individuals have taken meprobamate in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

Included within the term "hazard" are:

a. Use of meprobamate to achieve intoxication;

b. Use of meprobamate to attempt suicide, successfully or unsuccessfully.

Meprobamate when taken by certain types of individuals in amounts in excess of six 400-milligram tablets per day, has produced in the past and will produce intoxication marked by slurred speech, incoordination, pleasurable feelings simulating alcoholic intoxication (sometimes referred to as euphoria) and nystagmus. While the complex psychological reasons which induce some individuals to ingest intoxicating doses of depressant drugs are not known, it is known that individuals with drug-dependency-prone per-

sonalities (immature, neurotic, inadequate, dependent-type personalities) will chronically ingest drugs which produce euphoria, variously described as exaggerated feelings of well-being not in conformity with reality, feelings of happiness or elevation of mood, the relaxation and relief of tensions caused by psychological stress, a general dulling of the sensorium, or a sense of intoxication. Meprobamate causes these effects through its pharmacological action upon the central nervous system. Such effects have been reported by the ingestion of a single dose of meprobamate of 1,200 to 1,600 milligrams; however, with chronic ingestion of meprobamate a tolerance to its effects develops. Tolerance is a physiological process whereby an organism develops insensitivity to a drug, thus requiring the administration of gradually increasing doses in order to achieve the initial effect. It is believed that tolerance occurs when the body gradually adapts to the presence of a drug by altering the functions of certain systems and by increasing the rate at which the drug is metabolized. Thus, in order to achieve the initial physiological response, increasingly larger doses of the drug need to be ingested. Clinical observation together with data derived from animal experiments conclusively establish that meprobamate is a drug to which a tolerance is built when taken over extended periods of time. It is because such a tolerance is established that some individuals, in an attempt to relieve their symptoms of anxiety, will gradually increase the amounts of meprobamate they ingest to the point of intoxication. (TR. 40, 45, 86, 87, 106, 107, 135, 234-244, 261-262, 330-334, 462-463, 469, 484, 499, 504, 511-514, 586, 611-612, 795, 823-842, 875-881, 897-904, 993, 1836, 2744, 4033-4034, 4383-4386, 4698-4721; G. Ex. 19, 29, 49, 68, 71, 83, 97, 171, 179.)

Findings of Fact and Conclusions of Law

9. The substantial evidence of record establishes that persons have consumed meprobamate in amounts sufficient to cause chronic intoxication. Consumption by individuals of meprobamate in this manner is generally characterized by:

a. Staggering gait, slurred speech, and incoordination as well as temporary loss of memory and dulling of mental capacities. (TR. 504-514, 823-841, 875-881; G. Ex. 29, 49, 78, 83, 171.)

b. Ingestion of the drug in daily dosages in excess of those recommended for therapeutic use and varying generally between 8 and 50 400-milligram tablets daily. (TR. 504-514, 741-780, 823-841, 875-881; G. Ex. 29, 49, 52A; 74, 77, 79.)

c. A gradual elevation by individuals of their drug intake from prescribed dosage levels to levels which cause intoxication. (TR. 234-248, 260-262, 311-316, 504-514, 747, 798, 817-844; G. Ex. 29, 178, 179, 186.)

10. The substantial evidence of record shows that the chronic ingestion of meprobamate at intoxicating dosage levels deprives individuals of the ability to properly operate motor vehicles and to prevent injury to themselves and others. TR. 190-194, 248, 504-508; G. Ex. 18, 163.)

11. The substantial evidence of record shows that the chronic ingestion of meprobamate at intoxicating dosage levels causes personality changes in the users manifested by anger, antagonism, irrational behavior, and antisocial conduct. Such ingestion of this drug has led to the commission of crimes, neglect of children, and deterioration of marital and family relationships. (TR. 246, 509-510, 767,

1127-1147, 1334-1363, 1364-1390, 1390-1402; G. Ex. 29, 49, 54, 55, 58, 68, 73, 77, 79, 163.)

12. The substantial evidence of record shows that individuals consume meprobamate in intoxicating doses in order to achieve a mental condition that has been described as pleasurable and to achieve a feeling or sense of intoxication or well-being. This condition simulates intoxication caused by the ingestion of excessive amounts of alcohol or barbiturates. A significant number of individuals who have a propensity for becoming dependent on certain types of drugs, have found that they can take meprobamate in increasing doses and obtain somewhat the same effect that they get from alcohol or barbiturates. The most prominent group of such individuals are alcoholics. It has been observed by qualified and reliable experts in the field of alcoholism treatment that alcoholic patients have a particular liking for meprobamate and have repeatedly asked for this drug at more frequent intervals than for other drugs.

Because of these factors, alcoholics tend to become dependent on and to abuse meprobamate. Meprobamate presents special problems for the alcoholic population of this country, which has been estimated to number approximately 6 million. One conservative estimate is that four out of every 100 alcoholics to whom meprobamate is administered develop problems with meprobamate by taking to the point of intoxication more than prescribed. The potentiality for significant abuse presented by these reliable estimates is obvious. (TR. 35-38, 195-197, 234-248, 260-262, 288-289, 296-297, 311-316, 323-334, 488-519, 525-564, 559, 762, 1334-1350, 1523-1548; G. Ex. 20, 79, 171, 178, 179.)

13. Clinical experience shows that the prolonged use of meprobamate, even at therapeutic dose levels, causes or aggravates depressive states in certain individuals suffering from neurotic disorders. Persons who have chronically ingested meprobamate report that the psychological effect of the drug upon them was an aggravation of a feeling of depression to the point of suicidal thoughts and suicidal attempts. Medical experts are of the opinion that meprobamate and other tranquilizing drugs of similar types have a pharmacological effect which may either cause depression or aggravate a preexisting, underlying depressive state that may lead to suicide. (Tr. 238-249, 1422-1435, 1453-1455, 2765, 2786, 3370, 3594; G. Ex. 63, 79, 83, 110, 111.)

14. The substantial evidence of record conclusively establishes that a significant number of individuals have used meprobamate as an ingestant either alone or in combination with other depressant drugs, for the purpose of committing suicide. (TR. 661-699, 1163-1164, 1427, 1430-1456, 2124, 2727-2729, 3114-3115, 3885-3886, 4632-4639; G. Ex. 30-42, 44-47, 86-88, 90, 94, 97, 112, 117, 119, 122, 126, 129, 163, 182.)

15. The substantial evidence of record conclusively establishes that meprobamate either alone or in combination with other depressant drugs has been used by a significant number of individuals in suicidal attempts. (TR. 214-216, 363-366, 2124, 3114-3115; G. Ex. 8, 55, 68, 71, 87-89, 91, 92, 94, 104, 106, 108, 110, 111, 164, 166, 188, 192, 194, 195, 198, 199.)

16. The sociological reasons why meprobamate has been used in the past by a significant number of individuals

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in successful and unsuccessful suicidal attempts were, in part at least, explained by an expert in the field of public health and preventive medicine. This expert has studied extensively and written on the phenomena of suicide both in this country and many foreign lands.

There are three major sociological or cultural factors that operate in determining the manner and means used by individuals in suicidal gestures. These are the gross availability, accessibility and fashionability of agents used to commit suicide. Gross availability was explained to mean the presence of the agent in an individual's environment; for example, firearms are grossly available in the United States but not so available in other foreign countries, such as England. Accessibility was defined to mean the degree of ease by which individuals can obtain any given agent which is grossly available. Fashionability was defined as the popularity of any given agent as a suicidal agent which is determined in part by the frequency that an agent is used by society's ostensible leaders and the publicity accorded the suicides of such individuals. As far as pharmaceutical suicidal agents are concerned, factors such as frequency that a drug is prescribed, the length of time that a drug has been available, and the practice of pharmacists in making the drug available, as well as the knowledge of the lay population of these factors, exert influences on the frequency that a pharmaceutical agent is used in suicidal gestures.

The evidence of record clearly establishes that for the past decade in the United States meprobamate has been manufactured and distributed in large quantities; the respondent's estimate is approximately 14 billion tablets. Thus mepromabate has been grossly available. In addition, this drug has been widely prescribed during this time;

the respondent estimates that approximately 500 million prescriptions have been written for meprobamate. Further, meprobamate has to a significant extent been prescribed and dispensed with considerable laxity in the past (see Findings Nos. 18, 19, and 21). Meprobamate thus has been accessible. Its use as a suicidal agent has also received publicity, and its use as such an agent is thus known to the lay population.

Based upon the above considerations, as well as past studies of suicidal agents of the ingestant class, this expert made an authoritative prediction, which is reasonable and merits weight in this matter that meprobamate will be used more frequently in the future as a suicidal agent than it has been in the past. This prediction is based in major part on the past history of other pharmaceutical agents, notably the barbiturates. The longer these agents were on the market (grossly available), and the more accessible they became to potential suicidal individuals through lax dispensing and prescribing practices (accessibility), and the more the lay population learned of the use of these agents in suicidal gestures through the publicity afforded such cases (fashionability), the more such agents have been used in suicidal gestures.

It is reasonable to expect that meprobamate will have somewhat the same history as these other agents, notably the barbiturates, unless it is placed under the same controls. Although the barbiturates in the past have been the drugs most frequently used as suicidal ingestants, tranquilizing drugs are being used with increasing frequency and, among the latter, meprobamate is the drug most frequently used by suicide-prone individuals. (TR. 410-453, 712-713; G. Ex. 44, 55, 71, 83, 145, 165, 177, 202.)

17. The second criterion contained in the regulations promulgated under the amendments to be used to determine whether a substance has a potential for abuse because of its depressant effect on the central nervous system states, in substance, that a drug may have a potential for abuse if there is significant diversion of the drug from legitimate drug channels (see Finding No. 7).

Included within the term "diversion" are sales of a drug outside legitimate channels by manufacturers, wholesalers, or retail pharmacies. Thus, the sale of meprobamate by a retail pharmacy without the required prescription and not in complete conformity with the law regulating the sale of drugs restricted to sale only upon prescription (21 U.S.C. 353(b)) constitutes diversion of this drug from legitimate drug channels because such sales are contrary to law and are illegitimate. (G. Ex. 2, p. 2; 21 U.S.C. 331(k), 353(b).)

18. The substantial evidence of record conclusively proves that there has been significant diversion of meprobamate from legitimate drug channels. Substantial amounts of meprobamate have been sold by retail pharmacists without proper prescription authorization and not in conformity with those provisions of law regulating the sale of prescription drugs. The official files of the Food and Drug Administration were reviewed for the 10-year period from 1956 through 1966. The information contained therein relevant to meprobamate was testified to by an Administration official and summarized in Government Exhibit No. 202.

During this 10-year period, there were 1,515 prosecutions for illegal sales of prescription drugs terminated by convictions after initial investigation by the Food and Drug Administration. Of these cases, 173 involved 797

separate illegitimate sales of meprobamate to individuals, the sales being made either without any prescription or by refilling a prescription without proper authorization confirmed by a written record of the transaction as required by law. These illegitimate sales were made at 170 different retail pharmacies throughout the United States, by two peddlers, and by one medical doctor outside a doctor-patient relationship.

At 99 of the 170 retail pharmacies, investigators were permitted to audit the prescription dispensing records required to be maintained by law (21 U.S.C. 353(b), as well as invoices reflecting the amounts of prescription drugs received at these establishments. These records were audited for approximately a 1-year period prior to the time that this audit inspection took place. In 71 of the retail pharmacies, no audit was conducted because permission to review the necessary records was denied the investigators.

In the 99 drugstores where an audit was conducted, a comparison of the amounts of meprobamate received at the stores (as reflected by drug invoice records) with the amounts on hand at the stores and the amounts accounted for by prescription dispensing records, for the approximate 1-year period, showed that between 22 percent and 100 percent of the meprobamate received by these pharmacies could not be accounted for. Since meprobamate may be legitimately dispensed only upon prescription, and since the law requires the maintenance of records reflecting the dispensing of prescription drugs, the conclusion follows that the unaccounted for meprobamate was either sold without proper prescriptions or no records were maintained of prescription sales as required by law. In either case, the sales were illegitimate and represented a diversion of meprobamate from legitimate drug channels.

An average of 77 percent of the total amount of meprobamate received by these 99 pharmacies could not be accounted for. This 77-percent-average shortage represents over 796,000 tablets of meprobamate. The significance of this shortage is apparent when it is recalled that these audits covered approximately a 1-year period in but 99 retail pharmacies in this country.

Of these unaccounted for drugs, 54,128 meprobamate tablets were purchased by agents of the Food and Drug Administration, posing as ordinary drugstore customers, either without any prescription or by having a prescription illegally refilled. (TR. 1180-1333; G. Ex. 202.)

19. There is substantial evidence of record that some pharmacists have dispensed meprobamate on the basis of invalid prescriptions, or without any prescription at all. (TR. 510-511, 515, 525-564, 823-841, 1127-1161; G. Ex. 54, 135, 137, 138, 165, 180, 181.)

20. There is substantial evidence of record that there are so-called black market sources for meprobamate. These sources, which are not legitimate distributors, are utilized by individuals who have become dependent upon meprobamate to obtain supplies adequate to satisfy their needs. Individuals who report obtaining this drug from these sources are vague and indefinite about these sources and no detailed information is available as to the extent or number of such sources. There is also evidence that meprobamate has been stolen from hospital supplies for purposes of resale, and is bought and sold, illegitimately, by the inmates in penal institutions. (TR. 332-333, 347-349, 993, 996; G. Ex. 49, 131, 132.)

21. The substantial evidence of record shows that a significant number of individuals have obtained meprobamate in amounts in excess of the amounts prescribed for them or without the advice of their physician or in amounts in excess of recommended doses, in the following ways:

a. Through the lax prescribing practices of some physicians in issuing prescriptions which may be refilled for indefinite time periods at the option of the patient and because of the lack of supervision of patients by some physicians. (TR. 509-518, 525-549, 794, 904-907, 994, 1334-1350, 1364-1384, 1404-1421; G. Ex. 44, 55, 71, 83, 165.)

b. By having refilled prescriptions marked "Ad Lib." (Ad Libitum—the amount desired) and "p.r.n." (pro re nata—as circumstances may require) with greater frequency than is consistent with the use of the drug at recommended dosages. (TR. 197-202, 518, 525-549, 904, 1407-1408, 1416; G. Ex. 180, 181.)

c. By establishing a chain or series of drugstores which will sell them the drug. This is accomplished by taking a prescription to one drugstore, having it filled at this store, and then going to a series of other drugstores and asking each successive store to sell meprobamate to them. These additional drugstores are referred to the original store to verify that a prescription has been filed at that store. These successive stores then sell the drug based on the prescription filed at the original store. (TR. 525-549; G. Ex. 21, 29, 55, 180, 181.)

d. By obtaining a number of concurrent prescriptions for meprobamate from several physicians. (TR. 190-194, 245, 514, 518, 766, 875-881, 943, 967; G. Ex. 29, 77, 79.)

e. By obtaining meprobamate from friends or relatives for whom it had been prescribed. (TR. 190-194, 942-943, 1528-1530; G. Ex. 54.)

f. Through theft of the drug and by forging prescriptions for it. (TR. 511, 3006-3007; G. Ex. 58, 67, 68.)

22. The substantial evidence shows that meprobamate has been found in human subjects at autopsy by reliable toxicological examination and that routine, official investigation could not establish that the drug was taken upon the recommendation of a medical practitioner. The evidence further shows that pharmacists are frequently requested to sell meprobamate without any prescription, and indiviuals have offered to pay physicians for prescriptions for meprobamate without any bona fide doctor-patient relationship being established. Patients admitted to hospitals with meprobamate in their possession have refused to reveal their source for this drug. (TR. 661-710, 716-732, 965-967, 1409-1410, 1416, 1419; G. Ex. 84, 182.)

23. The substantial evidence of record conclusively establishes that a significant number of individuals have taken meprobamate on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer this drug in the course of his professional practice. Thus, the evidence of record complies with the third criterion set forth in the regulations promulgated under the Amendments (see Finding No. 7). Although the exact number of individuals who have abused meprobamate is not known, nor can this number be reasonably ascertained with any degree of reliability for the reasons more fully set forth in Finding No. 27, the number of suicides, attempted suicides, and overdoses of meprobamate reflected in the reliable evidence of record is significant.

An official of the Food and Drug Administration appeared and testified concerning Government Exhibit No. 87. This exhibit is a compilation of data contained in the official files of the Administration. This data includes photographic reproductions of death certificates submitted by the Departments of Health for 34 States, plus reports from approximately 350 of the 500 Poison Control Centers in the United States. The data summarized in Government Exhibit No. 87 shows that for a period of approximately 2 years (1964-65), meprobamate was found to be the exclusive or contributing cause of death in 92 suicides and 784 attempted suicides or accidental overdosages.

In addition, the testimony of the chief toxicologist for only one major city in the United States, Philadelphia, when studied in relation to Government Exhibit No. 182, a compilation of data contained in the official files of that city's Department of Health, reflects that for approximately a 4-year period meprobamate contributed to or was the exclusive cause of death in 37 suicides, plus 4 additional deaths that apparently were suicides but which may have been accidental deaths due to overdosage of drugs including meprobamate. Further, Government Exhibits Nos. 31-42, consisting of copies of the coroner's verdict for Cuyahoga County in Ohio for a 4-year period, reflect an additional 12 cases of suicides caused by the acute intoxication of the deceased by meprobamate alone or in combination with other drugs.

The testimony of these witnesses, together with the exhibits referred to above, when coupled with the testimony of individuals who have become physically dependent upon meprobamate, and the expert opinions and factual testimony of the Government's medical witnesses, establishes beyond any doubt that meprobamate has been abused in the

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past by a significant number of individuals in that they have taken this drug on their own initiative and contrary to medical advice, to their own detriment to the point of death. (TR. 661-732, 1162-1178, 1334-1389, 1390-1402, 3950-4102, 4256-4444, 4449-4505; G. Ex. 87, 182 (see also G. Ex. 30-42, 44-47, 8, 55, 68, 71, 86, 88, 89-91, 104, 106, 108, 112, 117, 119, 122, 126, 129, 163, 164.)

24. The evidence of record reflects the testimony of medical experts that drugs which depress the activity of the central nervous system when administered over long periods of time may cause certain neuronal systems to adapt their activity to the effect of the drug so that upon abrupt withdrawal of the drug, clinically observable signs and symptoms may result that are associated with acute psychological and physical discomfort or death. This phenomenon, known as an abstinence reaction or withdrawal syndrome, is a sign of a tolerance being established in the body to the drug and is indicative of physical dependence upon the drug. Individuals are motivated to ingest drugs in increasingly larger amounts, upon their own initiative or without medical supervision, in order to avoid experiencing this withdrawal syndrome.

Physical dependence is the result of the chronic ingestion of a drug at sufficiently high dosage levels, and in the case of meprobamate, does not generally manifest itself until after prolonged ingestion in man of daily dosages exceeding eight 400-milligram tablets, although occurrences of withdrawal symptoms at lesser dose levels have been observed. Due to individual variation in convulsion threshold levels, differences in personality structures, metabolic rates and capacities, and other physiological differences, no physically dependent person may display the entire spec-

trum of withdrawal symptoms upon the abrupt withdrawal of meprobamate. However, the sudden withdrawal of this drug after chronic ingestion at the dosages noted above is generally characterized in cases of mild physical dependence by insomnia, vomiting, tremors, muscle twitching, anxiety, weakness, nausea, headache, hyperpyrexia, anorexia, and ataxia. In cases of moderate physical dependence, the withdrawal symptoms include also hallucinations, delusions, and severe depression. The severe form of withdrawal symptoms additionally include convulsions and in rare instances death. (TR. 34-51, 312, 314, 478-482, 585-605, 796, 917-918, 3370, 3379, 3380, 4690, 4696-4698, 4701-4702, 4704-4706; G. Ex. 12, 19, 20, 24, 28, 29, 131, 133, 150, 162, 200, 201.)

25. The substantial evidence of record shows that individuals who have ingested meprobamate over prolonged periods of time upon their own initiative, or who have on their own initiative increased their dosage of meprobamate to levels in excess of those normally prescribed and recommended, have upon abstinence from the drug suffered the following withdrawal symptoms: Electroencephalographic changes similar to those observed in barbiturate withdrawal, headaches, insomnia, nervousness and anxiety, agitation and restlessness, sweating, ataxia, nausea, excess salivation and confusion, delirium, delusions and hallucinations, hyperpyrexia, convulsions, and death. (TR. 186-187, 493-494, 508-519, 525-549, 575-587, 823-841, 875-881, 1127-1138, 1334-1350, 1390-1398, 1426, 2397, 4758; G. Ex. 16, 17, 21, 23, 28, 29, 63, 81, 82, 84, 94, 150, 166, 171, 185, 186, 193, 204.)

26. The substantial evidence of record shows that some individuals who are abusing barbiturates or alcohol also

concurrently abuse meprobamate, or if their drug of choice becomes unavailable, will turn to meprobamate. The abusive use of meprobamate results from the interaction of two factors, the pharmacological action of the drug and the psychological makeup of the individual. Dependency-prone individuals having immature, neurotic, or inadequate, dependent-type personalities, especially those with a history of dependency upon other drugs, are particularly liable to become dependent upon meprobamate. Thus, alcoholics are particularly susceptible to dependency upon and abusive use of meprobamate.

The likelihood of the cross-substitution of drugs having similar clinical and pharmacological effects may be determined with a reasonable degree of accuracy on the basis of similarity of withdrawal symptoms and the ability of one drug to suppress the withdrawal symptoms caused by the abrupt withdrawal of another. The substantial evidence of record shows that intoxication caused by meprobamate is clinically and, except for minor differences, neurophysiologically indistinguishable from intoxication caused by alcohol or barbiturates.

The withdrawal symptoms associated with meprobamate are similar to those associated with drugs causing a barbiturate and alcohol-type physical dependence; such as, the barbiturates, ethyl alcohol, chloralhydrate, paraldehyde, and glutethimide.

It has been demonstrated that barbiturates, if administered in appropriate doses, will completely relieve the withdrawal symptoms caused by the abrupt cessation of meprobamate ingestion and that meprobamate will suppress the withdrawal symptoms caused by the cessation of excessive alcohol ingestion.

There is, therefore, the reasonable likelihood that when drugs of the barbiturate-alcohol type become less accessible because of more strict control of their distribution under the Amendments, individuals who have abused this type of drug will substitute meprobamate in their nontherapeutic, abusive drug practices. (TR. 38, 47, 49, 79-81, 86-87, 195-197, 210, 238-243, 312-313, 330-331, 461-465, 467-468, 473-475, 478-482, 508, 515, 583, 585-586, 590-595, 599-605, 796, 851, 854-855, 918-921, 933-947, 989, 1527-1548, 4690-4695, 4697, 4703-4705, 4724-4725, 4758; G. Ex. 1, 16, 23, 28, 29, 65, 78, 84, 131, 132, 133, 145, 150, 162, 171.)

27. There are at the present time no reliable statistics which indicate with certainty the precise extent to which meprobamate has been or is currently being abused. Hospital records are customarily coded, for purposes of indexing and information retrieval, by discharge diagnoses, not admission diagnoses. In many cases of admission for drug overdose or drug dependence, the discharge diagnosis will show the underlying psychiatric disorder that gave rise to the individual's suicide attempt or chronic use of drugs, but not the drug abuse which led to admission. There are no accurate statistics showing the extent to which meprobamate is used in suicidal attempts, successful or unsuccessful, on either the local, State, or national level. Death certificates, one possible source of such statistics, are issued in many cases immediately after death in order to permit burial of the deceased, but prior to toxicological examination that would reveal the presence of exogenous agents in the vital organs of the deceased. No consistent practice is followed in amending such records where exogenous agents are found upon examination. Thus, the statistics of State bureaus of vital statistics, based upon such death

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certificates, do not reveal the presence of such agents in a large number of cases. National vital statistics, having as their source the State statistics, are equally inadequate. The lack of trained and experienced personnel, adequate funds, and adequate coding and indexing systems, in the nation's hospitals, bureaus of vital statistics, health departments, and other public and private institutions all contribute to the lack of accurate statistics concerning meprobamate abuse. The statistics that are available grossly understate the frequency with which meprobamate has actually been abused. (TR. 360-369, 383-388, 404-409, 434-435, 608-610, 632-633, 777, 797, 941-942, 958-959, 1428-1430, 1709, 1711-1712, 2771, 2972-2973, 3661-3665, 3671, 3683, 3696, 3709, 3718-3720, 3733, 3744-3747, 3942-3953, 3958-3959, 3968, 3989, 3991, 4059, 4272, 4294-4297, 4367-4375, 4398-4399, 4425-4429, 4441, 4450, 4459; G. Ex. 62 pp. 54-56.)

28. The substantial evidence of record establishes that meprobamate has a potential for abuse, as manifested in the ways set forth in findings 8 through 27 above, because of its depressant effect on the central nervous system. Many of these abuses of meprobamate result from the phenomenon of tolerance to the drug and the phenomenon of withdrawal reactions upon discontinuance after long-continued or excess use. These phenomena of tolerance and withdrawal reactions are a result of meprobamate's central nervous system depressant effect. Other abuses of meprobamate stem from its euphoric effect which is a function of meprobamate's central nervous system depressant effect. In short, meprobamate's potential for abuse results from its effect of depression on the central nervous system. (TR. 21, 49, 81, 98, 334, 402-463, 478, 3359-3360, 3425-3426, 4698-4709.)

Findings of Fact and Conclusions of Law

29. A large part of the evidence adduced by the respondent consisted of the testimony of various physicians to the effect that they had prescribed meprobamate for their patients over varying periods of time and had seen no cases or at most only an occasional case of individuals abusing meprobamate. This evidence does not rebut the evidence introduced by the Government proving the abuse potential of meprobamate within the meaning of the amendments. The doctors appearing on behalf of the respondent were administering meprobamate generally at therapeutic dosage levels not in excess of recommended doses and were closely supervising the drug therapy of their patients. Patients under such close medical supervision do not usually abuse meprobamate. In addition, some physicians appearing as witnesses for the respondent were involved in various specialties of medicine in which meprobamate abuse is rarely if ever seen; such as, cardiology, general surgery, obstetrics, gynecology, endocrinology, gerontology, gastroenterology, otorhinolaryngology, and allergy.

Such evidence tends to confirm the following estimation set forth in the Final Report of the President's Advisory Commission on Narcotic and Drug Abuse of 1963: "Drug abuse is not a uniform problem throughout the country, and even in the areas of the highest incidence few medical practitioners come into contact with the afflicted. It is estimated that most medical practitioners never see a habitual drug abuser" (G. Ex. 1, p. 57). (TR. 1934-1944, 1960-1970, 2339-2346, 3182-3187, 3361, 3429-3433, 3515-3523, 3606-3620.)

30. The legislative history of the amendments reflects the expectation of Congress, in enacting this legislation, that meprobamate and similar tranquilizing drugs would be

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expeditiously brought under the control of the amendments because of their potential for abuse. Testimony taken before the House Committee on Interstate and Foreign Commerce demonstrated the need for bringing meprobamate under these controls. This Committee considered the advisability of listing meprobamate, among others, by name, but decided not to single out this or any other drug. The Committee, however, stated that it expected the Secretary of Health, Education, and Welfare to take early action with respect to the consideration of bringing meprobamate and other drugs within the controls of the amendments. A similar expectation was expressed by the Senate Committee on Labor and Public Welfare. (G. Ex. 62, pp. 24, 26, 33-36, 49-51, 54, 93, 102-103; 115; G. Ex. 2, p. 13; G. Ex. 3, pp. 2 and 3.)

Conclusions. 1. The Drug Abuse Control Amendments of 1965 are intended to protect the public health and safety by establishing special controls for depressant and stimulant drugs. This protection is to be accomplished through increased recordkeeping and inspection requirements, through providing for control over intrastate traffic in these drugs because of its effect on interstate traffic, and through making possession of these drugs (other than by the user) illegal outside the legitimate channels of commerce. The authority of the Department of Health, Education, and Welfare over counterfeit drugs also is increased by the amendments.

2. Meprobamate is a drug with a depressant effect on the central nervous system and may be legitimately dispensed only upon the prescription of a practitioner licensed by law to administer such drugs, and in full conformity with section 503(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)).

3. The substantial, probative, and reliable evidence of record establishes that meprobamate, in the past, due to its depressant effect on the central nervous system, has been abused in the following ways:

a. There has been significant use of meprobamate in amounts sufficient to create a hazard to the health of the individual and to the safety of other individuals and the community.

b. There has been significant diversion of meprobamate from legitimate drug channels.

c. There has been significant use of meprobamate by individuals on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

4. Due to the history of the abuse of meprobamate and because meprobamate has the capacity to substitute for other drugs known to be abused, which are now subject to the increased controls of the amendments, it is reasonable to conclude that the abuse of meprobamate will continue and increase unless this drug is similarly brought under the controls of the amendments.

5. Meprobamate is a drug which because of its depressant effect on the central nervous system has a substantial potential for significant abuse within the meaning of the amendments (21 U.S.C. 321(v)(3)).

6. Meprobamate is a "depressant or stimulant drug" as defined in the amendments (21 U.S.C. 321(v)), and is therefore subject to control under the amendments (21

U.S.C. (360a). Any drug which contains any quantity of meprobamate is a "depressant or stimulant drug" as defined in the amendments (21 U.S.C. 321(v)(3)) and is also subject to control under the amendments (21 U.S.C. 360a).

Therefore, It is ordered, That the stay of effectiveness announced May 17, 1966 (31 F.R. 7174), on the listing of meprobamate in §166.3(c)(1) as a drug subject to control under the amendments by the order of March 19, 1966 (31 F.R. 4679), be ended.

Effective date. This order shall become effective 90 days from its date of publication in the FEDERAL REGISTER.

(Secs. 201(v), 511, 701, 52 Stat. 1055, as amended, 79 Stat. 227 et seq.; 21 U.S.C. 321(v), 360a, 371)

Dated: November 28, 1967.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

APPENDIX D

Decree of the Court of Appeals

(Filed November 25, 1969)

UNITED STATES COURT OF APPEALS

FOR THE FOURTH CIRCUIT

No. 12,200

CARTER-WALLACE, INC.,

Petitioner,

vs.

JOHN W. GARDNER, Secretary of Health, Education and Welfare, and JAMES L. GODDARD, Commissioner of Food and Drugs,

Respondents.

ON PETITION to Review and Set Aside an Order of the Commissioner of Food and Drugs.

THIS CAUSE came on to be heard on the transcript of the record from The Commissioner of Food and Drugs, and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered, adjudged and decreed by this Court that the order of the said The Commissioner of Food and Drugs, in this cause, be, and the same is hereby, affirmed.

SAMUEL W. PHILLIPS
Clerk

Decree of the Court of Appeals

FILED

Nov 25 1969

SAMUEL W. PHILLIPS
CLERK

A True Copy, Teste:

SAMUEL W. PHILLIPS, *Clerk*
By /s/ JO ANN C. KIRKPATRICK
Deputy Clerk

APPENDIX E

Relevant Statutes and Regulations

The Administrative Procedure Act, 60 Stat. 243 (1946), 5 U.S.C. §551, *et seq.* (Public Law 89-554, 80 Stat. 378), provides in pertinent part:

§556. Hearings; presiding employees; powers and duties; burden of proof; evidence; record as basis of decision

* * *

(d) Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof. Any oral or documentary evidence may be received, but the agency as a matter of policy shall provide for the exclusion of irrelevant, immaterial, or unduly repetitious evidence. A sanction may not be imposed or rule or order issued except on consideration of the whole record or those parts thereof cited by a party and supported by and in accordance with the reliable, probative, and substantial evidence. A party is entitled to present his case or defense by oral or documentary evidence, to submit rebuttal evidence, and to conduct such cross-examination as may be required for a full and true disclosure of the facts.

* * *

§702. Right of review

A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof. * * *

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§704. Actions reviewable

Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review.

• • •

§706. Scope of review

To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall—

• • •

(2) hold unlawful and set aside agency action, findings, and conclusions found to be—

(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

• • •

(C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right;

(D) without observance of procedure required by law;

(E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute;

• • •

In making the foregoing determinations, the court shall review the whole record or those parts of it cited by a party,

and due account shall be taken of the rule of prejudicial error. • • •

The Federal Food, Drug and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 U.S.C. §301, *et seq.*, provides in pertinent part:

Section 201(v), 21 U.S.C. §321(v):

(v) The term "depressant or stimulant drug" means—

(1) any drug which contains any quantity of (A) barbituric acid or any of the salts of barbituric acid; or (B) any derivative of barbituric acid which has been designated by the Secretary under section 352 (d) of this title as habit forming;

(2) any drug which contains any quantity of (A) amphetamine or any of its optical isomers; (B) any salt of amphetamine or any salt of any optical isomer of amphetamine; or (C) any substance which the Secretary, after investigation, has found to be, and by regulation designated as, habit forming because of its stimulant effect on the central nervous system; or

(3) any drug which contains any quantity of a substance which the Secretary, after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect; except that the Secretary shall not designate under this paragraph, or under clause (C) of subparagraph (2), any substance that is now included, or is hereafter included, within the classifications stated in section 4731, and marijuana as defined in section 4761, of Title 26.

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The provisions of subsections (e), (f), and (g) of section 371 of this title shall apply to and govern proceedings for the issuance, amendment, or repeal of regulations under subparagraph (2) (C) or (3) of this paragraph. * * *

Section 511a, 21 U.S.C. §360a:

* * *

Records; inspection: right of agents to enter, notice, scope, inventory, receipt for samples taken; exemption of practitioners

(d) (1) Every person engaged in manufacturing, compounding, processing, selling, delivering, or otherwise disposing of any depressant or stimulant drug shall, upon the effective date of this section, prepare a complete and accurate record of all stocks of each such drug on hand and shall keep such record for three years. On and after the effective date of this section, every person manufacturing, compounding, or processing any depressant or stimulant drug shall prepare and keep, for not less than three years, a complete and accurate record of the kind and quantity of each such drug manufactured, compounded, or processed and the date of such manufacture, compounding, or processing; and every person selling, delivering, or otherwise disposing of any depressant or stimulant drug shall prepare or obtain, and keep for not less than three years, a complete and accurate record of the kind and quantity of each such drug received, sold, delivered, or otherwise disposed of, the name and address of the person, and the registration number, if any, assigned to such person by the Secretary pursuant to section 360(e) of this title, from whom it was received and to whom it was sold, delivered, or otherwise disposed of, and the date of such transaction. No separate

records, nor set form or forms for any of the foregoing records, shall be required as long as records containing the required information are available.

* * *

(3) The provisions of paragraphs (1) and (2) of this subsection shall not apply to a licensed practitioner described in subsection (a) (4) of this section with respect to any depressant or stimulant drug received, prepared, processed, administered, or dispensed by him in the course of his professional practice, unless such practitioner regularly engages in dispensing any such drug or drugs to his patients for which they are charged, either separately or together with charges for other professional services.

Prescriptions; limitation or refills; renewals

(e) No prescription (issued before or after the effective date of this section) for any depressant or stimulant drug may be filled or refilled more than six months after the date on which such prescription was issued and no such prescription which is authorized to be refilled may be refilled more than five times, except that any prescription for such a drug after six months after the date of issue or after being refilled five times may be renewed by the practitioner issuing it either in writing, or orally (if promptly reduced to writing and filed by the pharmacist filling it).

Exemption of certain drugs

(f) (1) The Secretary may by regulation exempt any depressant or stimulant drug from the application of all or part of this section when he finds that regulation of its manufacture, compounding, processing, possession, and disposition, as provided in this section or in such part thereof, is not necessary for the protection of the public health.

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(2) The Secretary shall by regulation exempt any depressant or stimulant drug from the application of this section, if—

* * *

(B) he finds that such drug includes one or more substances not having a depressant or stimulant effect on the central nervous system or a hallucinogenic effect and such substance or substances are present therein in such combination, quantity, proportion, or concentration as to prevent the substance or substances therein which do have such an effect from being ingested or absorbed in sufficient amounts or concentrations as, within the meaning of section 321(v) of this title, to—

(i) be habit forming because of their stimulant effect on the central nervous system, or

(ii) have a potential for abuse because of their depressant or stimulant effect on the central nervous system or their hallucinogenic effect.

(g) (1) The Secretary may, from time to time, appoint a committee of experts to advise him with regard to any of the following matters involved in determining whether a regulation under subparagraph (2) (C) or (3) of section 321(v) of this title should be proposed, issued, amended, or repealed: (A) whether or not the substance involved has a depressant or stimulant effect on the central nervous system or a hallucinogenic effect, (B) whether the substance involved has a potential for abuse because of its depressant or stimulant effect on the central nervous system, and (C) any other scientific question (as determined by the Secretary) which is pertinent to the determination of whether such substance should be designated by the Secretary pur-

suant to subparagraph (2) (C) or (3) of section 321(v) of this title. * * *

Section 701(e), 21 U.S.C. §371(e):

Procedure for establishment

(e) (1) Any action for the issuance, amendment, or repeal of any regulation under section 341, 343(j), 344(a), 346, 351(b), or 352(d) or (h), of this title shall be begun by a proposal made (A) by the Secretary on his own initiative, or (B) by petition of any interested person, showing reasonable grounds therefor, filed with the Secretary. The Secretary shall publish such proposal and shall afford all interested persons an opportunity to present their views thereon, orally or in writing. As soon as practicable thereafter, the Secretary shall by order act upon such proposal and shall make such order public. Except as provided in paragraph (2) of this subsection, the order shall become effective at such time as may be specified therein, but not prior to the day following the last day on which objections may be filed under such paragraph.

(2) On or before the thirtieth day after the date on which an order entered under paragraph (1) of this subsection is made public, any person who will be adversely affected by such order if placed in effect may file objections thereto with the Secretary, specifying with particularity the provisions of the order deemed objectionable, stating the grounds therefor, and requesting a public hearing upon such objections. * * *

(3) As soon as practicable after such request for a public hearing, the Secretary, after due notice, shall hold such a public hearing for the purpose of receiving evidence rele-

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vant and material to the issues raised by such objections. At the hearing, any interested person may be heard in person or by representative. As soon as practicable after completion of the hearing, the Secretary shall by order act upon such objections and make such order public. Such order shall be based only on substantial evidence of record at such hearing and shall set forth, as part of the order, detailed findings of fact on which the order is based. The Secretary shall specify in the order the date on which it shall take effect, except that it shall not be made to take effect prior to the ninetieth day after its publication unless the Secretary finds that emergency conditions exist necessitating an earlier effective date, in which event the Secretary shall specify in the order his findings as to such conditions. * * *

Section 701(f), 21 U.S.C. §371(f):

Review of order

(f) (1) In a case of actual controversy as to the validity of any order under subsection (e) of this section, any person who will be adversely affected by such order if placed in effect may at any time prior to the ninetieth day after such order is issued file a petition with the United States court of appeal for the circuit wherein such person resides or has his principal place of business, for a judicial review of such order. A copy of the petition shall be forthwith transmitted by the clerk of the court to the Secretary or other officer designated by him for that purpose. The Secretary thereupon shall file in the court the record of the proceedings on which the Secretary based his order, as provided in section 2112 of Title 28. * * *

(3) Upon the filing of the petition referred to in paragraph (1) of this subsection, the court shall have jurisdic-

tion to affirm the order, or to set it aside in whole or in part, temporarily or permanently. If the order of the Secretary refuses to issue, amend, or repeal a regulation and such order is not in accordance with law the court shall by its judgment order the Secretary to take action, with respect to such regulation, in accordance with law. The findings of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive.

(4) The judgment of the court affirming or setting aside, in whole or in part, any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in sections 346 and 347 of Title 28.

(5) Any action instituted under this subsection shall survive notwithstanding any change in the person occupying the office of Secretary or any vacancy in such office.

• • •

PART 166—DEPRESSANT AND STIMULANT DRUGS; DEFINITIONS, PROCEDURAL AND INTERPRETATIVE REGULATIONS (31 F.R. 1071)

Regulations Implementing Drug Abuse Control Amendments of 1965

In the matter of promulgating regulations to implement the provisions of the Drug Abuse Control Amendments of 1965:

Having considered the comments and suggestions filed in response to the notice of proposed rule making in the above-identified matter published in the FEDERAL REGISTER of December 18, 1965 (30 F.R. 15667), the Commissioner of Food and Drugs has concluded that the regulations should

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be issued as set forth below incorporating suggestions in whole or in part. Changes have been made in §§166.1(i), 166.2(e), 166.3, 166.5, 166.16(b), and 166.17.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(v), 511, 701, 52 Stat. 1055, as amended, 79 Stat. 227 et seq.; 21 U.S.C. 321 (v), 360a, 371), and under the authority delegated to the Commissioner by the Secretary of Health, Education, and Welfare (21 CFR 2.90), Part 166 is amended by adding thereto new sections as follows:

* * *

(e) The Commissioner may determine that a substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect if:

(1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or

(2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or

(3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice;

* * *

In the Supreme Court of the United States

OCTOBER TERM, 1969

No. 1436

CARTER-WALLACE, INC., PETITIONER

v.

ROBERT H. FINCH, SECRETARY OF HEALTH, EDUCATION, AND WELFARE AND CHARLES EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

OPINION BELOW

The opinion of the court of appeals (Pet. App. 1a-19a) is reported at 417 F. 2d 1086.

JURISDICTION

The judgment of the court of appeals was entered on November 25, 1969. On February 10, 1970, the Chief Justice extended the time for filing a petition

for a writ of certiorari to April 21, 1970, and on April 17 the petition was filed. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

QUESTIONS PRESENTED

1. Whether the evidence supports the ruling of the Commissioner of Food and Drugs that meprobamate is a depressant drug subject to control under the Federal Food, Drug and Cosmetic Act as amended by the Drug Abuse Control Amendments of 1965.

2. Whether the ruling as to meprobamate was properly made applicable to combination drugs containing meprobamate.

STATUTES INVOLVED

The pertinent statutes, 21 U.S.C. (Supp. IV) 321(v)(3), and 21 U.S.C. (Supp. IV) 360a(f)(2)(B)(ii), are set forth at pp. 70a and 73a of the petition.

STATEMENT

In July 1965, Congress amended the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 301 *et seq.*, to apply specific controls upon the manufacture, sale and distribution of "depressant or stimulant drugs." P.L. 89-74, 79 Stat. 226. This term was broadly defined to include—

> (3) any drug which contains any quantity of a substance which the Secretary [of Health, Education, and Welfare], after investigation, has found to have, and by regulation designates as having, a potential for abuse because of its de-

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pressant or stimulant effect on the central nervous system * * * [21 U.S.C. 321(v)(3)].

Pursuant to the authority set forth in the Drug Abuse Control Amendments of 1965, and delegated to the Commissioner of Food and Drugs (21 C.F.R. (1966 ed.) 2.90), on January 18, 1966, the Commissioner proposed the listing of meprobamate as a drug having a potential for abuse because of its depressant effect upon the central nervous system. The proposal sought to designate all drugs containing any amount of meprobamate (and 16 other drugs) as subject to the controls authorized by the 1965 Amendments. Interested persons were invited to submit their views in writing.

On March 19, 1966, the Commissioner issued an order designating meprobamate and all drugs containing meprobamate as subject to control under the Amendments (31 F.R. 4679). Petitioner, a pharmaceutical firm engaged through a subsidiary in the manufacture, sale and distribution of meprobamate under the brand name Miltown, and of certain drugs containing meprobamate as an ingredient, filed objections to the Commissioner's order. Following a hearing,[1] conducted intermittently from June 27 to September 16, 1966, the FDA Hearing Examiner, in a report dated January 13, 1967, found substantial evidence that meprobamate has a potential for abuse because of its depressant effect on the central nervous

[1] The 4,891-page transcript of the hearing has not been filed with the Clerk of this Court. Excerpts from it appear in Carter-Wallace's Appendix and Respondents' Appendix in the court of appeals, which are included in the record filed with this Court. In all, 62 witnesses, including 50 medical doctors, testified, and 142 exhibits were introduced in evidence. See Pet. App. 35a-36a.

system (Pet. App. 20a-34a). The examiner further found that, although the record did not include substantial evidence that petitioner's drug compounds containing meprobamate have a potential for abuse, the controls authorized by the pertinent statute, *supra*, also apply to the combination drugs (Pet. App. 33a-34a).

After additional oral argument, the Commissioner, on December 6, 1967, issued his "Findings of Fact and Conclusions of Law," dated November 28, 1967 (Pet. App. 35a-65a). Among the facts found therein by the Commissioner to have been established by "substantial evidence of record" were that meprobamate presents a health hazard when consumed excessively; that persons have consumed the drug in sufficient amounts to cause chronic intoxication; that chronic ingestion has also caused personality changes and has led to the commission of crimes, neglect of children, and deterioration of domestic relationships; that individuals who have a propensity to become addicted to a drug, and especially alcoholics, have taken meprobamate to satisfy their craving; that the drug has been used as a means of committing suicide; that substantial amounts of meprobamate have been unlawfully distributed either through regular channels (doctors and pharmacies) or in the black market; that individuals have used devious methods to obtain the drug from lawful distributors; that prolonged ingestion causes the body to build a tolerance, so that increased quantities are needed for the desired effect; that sudden withdrawal after chronic ingestion is characterized by certain symptoms, the severity of which depends upon the degree of dependency on the drug; and

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that individuals who are addicted to certain other drugs and alcohol will turn to meprobamate if their supply of their primary drug is cut off. Accordingly, the Commissioner concluded (Pet. App. 64a-65a):

> 5. Meprobamate is a drug which because of its depressant effect on the central nervous system has a substantial potential for significant abuse within the meaning of the amendments (21 U.S.C. 321(v)(3)).
>
> 6. Meprobamate is a "depressant or stimulant drug" as defined in the amendments * * *, and is therefore subject to control under the amendments (21 U.S.C. 360a). Any drug which contains any quantity of meprobamate is a "depressant or stimulant drug" as defined in the amendments * * * and is also subject to control under the amendments * * *.

In the court of appeals petitioner acknowledged that meprobamate has a potential for abuse, but argued that the evidence failed to support the Commissioner's finding that the potential for abuse is connected to meprobamate's depressant effect on the central nervous system. In addition, petitioner alleged that its drugs containing meprobamate combined with others should not have been included in the order because of a lack of evidence that they have a substantial potential for significant abuse. Finally, petitioner charged bias on the part of the hearing examiner, as demonstrated particularly by his evidentiary rulings. The court of appeals rejected these contentions and affirmed the Commissioner's order (Pet. App. 1a-19a).

ARGUMENT

1. In this Court petitioner does not assail the fairness of the hearing examiner, but renews his attack

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upon the soundness of the Commissioner's findings relative to the depressant effect of meprobamate upon the central nervous system and the inclusion of the combination drugs in his control order. In petitioner's view, when the opinions of government witnesses are balanced against the conflicting opinions furnished by its witnesses, the standard of "substantial evidence" required to sustain the Commissioner's ruling has not been met.

The opinion of the court of appeals discusses this claim at length. The court recognized that the precise reason why meprobamate affects users as it does cannot be fully explained in the current state of scientific knowledge, so that expert opinions differ on how the drug operates. The experts agree, however, that the drug acts upon individuals very similarly to barbiturates and alcohol, which are known to have depressant effects upon the central nervous system. For example, excessive use of meprobamate can cause physical dependence, euphoria, and withdrawal symptoms similar to those caused by barbiturates and alcohol. And, as with these other depressants, the body reacts to continued consumption of meprobamate by building a tolerance, so that an increased dosage becomes necessary to produce the desired effect. Finally, there is evidence that meprobamate suppresses symptoms of withdrawal from alcohol and barbiturates; in other words, a cross-tolerance can be developed between meprobamate and other depressants. Drug-prone alcoholics, of which there are a substantial number in the United States, are likely to abuse meprobamate if given easy access to it. With these facts established by the record, there is indeed substantial

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evidence to support the findings of the Commissioner and his consequent conclusion, affirmed by the court of appeals, that meprobamate has a depressant effect on the central nervous system, and therefore has a potential for significant abuse within the meaning of the Drug Abuse Control Amendments of 1965.

This is not a case where, as petitioner contends, the court of appeals failed to review the entire record, or where the evidence given credence does not amount to "substantial evidence" (Pet. 13). As petitioner itself notes, the court of appeals opinion refers to the conflict between the testimony of witnesses for Carter-Wallace and that of government witnesses. At most, the situation presented was one where the fact-finder was called upon to resolve conflicts of expert opinion. His resolution of the conflicts against petitioner provides no occasion for review since the evidence relied upon was credible and the inferences drawn were reasonable. *Santa Fe Drilling Co.* v. *National Labor Relations Board*, 416 F. 2d 725, 730 (C.A. 9); *Erickson* v. *Federal Trade Commission*, 272 F. 2d 318 (C.A. 7), certiorari denied, 362 U.S. 940.

2. Since the determination that meprobamate was a drug subject to control under 21 U.S.C. 321(v)(3) was proper, the Commissioner's order necessarily applied to drug combinations which include meprobamate as an ingredient. This is so because the pertinent statutory definition, *supra*, embraces the primary drug and "any drug which contains any quantity" of the drug found to have a potential for abuse. Petitioner is not, however, precluded from securing an exception to the application of the Commissioner's or-

der, if one is desired and warranted. This can be done by instituting proceedings for an exemption under 21 U.S.C. 360a(f)(2), and establishing affirmatively that the amount of meprobamate contained in the combination drugs is not sufficient to regard them as having a potential for abuse because of their depressant effect on the central nervous system. Contrary to petitioner's contention, the hearing examiner's statement that there was a "lack of substantial evidence" in the record of the abuse potential of the combination drugs (Pet. 15; Pet. App. 33a) is not a substitute for an affirmative finding that the combination drugs qualify for exemption. The hearings to date obviously were not directed toward the combination products, and detailed evidence was not introduced on this question because a determination of abuse potential as to meprobamate itself was necessary before any issue regarding the combinations arose.

CONCLUSION

For the reasons stated, it is respectfully submitted that the petition for a writ of certiorari should be denied.

ERWIN N. GRISWOLD,
Solicitor General.

WILL WILSON,
Assistant Attorney General.

BEATRICE ROSENBERG,
MERVYN HAMBURG,
Attorneys.

MAY 1970.

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